## *United States Court of Appeals*
## *for the*
## *District of Columbia Circuit*

# TRANSCRIPT OF RECORD

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# BRIEF FOR APPELLANT AND APPENDIX

IN THE

# United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

## No. 14,181

968

C. H. BOEHRINGER SOHN, a Partnership, *Appellant*,

v.

ROBERT C. WATSON, Commissioner of Patents, *Appellee.*

**Appeal from the United States District Court for the District of Columbia**

United States Court of Appeals
For the
District of Columbia Circuit
FILED NOV 25 1957
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CLERK

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## STATEMENT OF QUESTION PRESENTED

Is one particular member of a series of chemical compounds, which member has unexpected and unobvious advantageous properties as compared with previously known members of the series, unpatentable simply because other members of the series are known and because a skilled chemist would have been able to prepare the member in question?

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IN THE

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FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 14,181

C. H. BOEHRINGER SOHN, a Partnership, *Appellant,*

v.

ROBERT C. WATSON, Commissioner of Patents, *Appellee.*

**Appeal from the United States District Court for the District of Columbia**

## BRIEF FOR APPELLANT

### JURISDICTIONAL STATEMENT

Plaintiff, a German partnership, filed on July 13, 1955 a complaint under 35 U.S.C. § 145 (Tr. 1-3) in the District Court of the United States for the District of Columbia against defendant as Commissioner of Patents, asking the

Court to authorize the issuance of a patent on its application Serial No. 251,840, filed October 17, 1951. The decision of the Board of Appeals of the Patent Office was rendered on May 16, 1955. (Tr. 81) After a judgment (Tr. 57) of the District Court dismissing the complaint, signed on May 6, 1957, plaintiff on May 16, 1957 moved for modification of the judgment (Tr. 57). This motion was denied on June 10, 1957, (Tr. 59) and a notice[4] of appeal to this Court was filed on August 6, 1957. (Tr. 59) Jurisdiction lies in this Court under 28 U.S.C. §§ 1291, 1294.

## STATEMENT OF CASE

Plaintiff, a German partnership, as assignee of Franz Adickes, regularly filed an application Serial No. 251,840 in the United States Patent Office on October 17, 1951. (Plaintiff's Exhibit 1, Tr. 61) The subject matter of the application was Process for the Production of Scopolamine Bromobutylate. The Examiner finally rejected the claims of the application, on the basis of certain prior patents, namely:

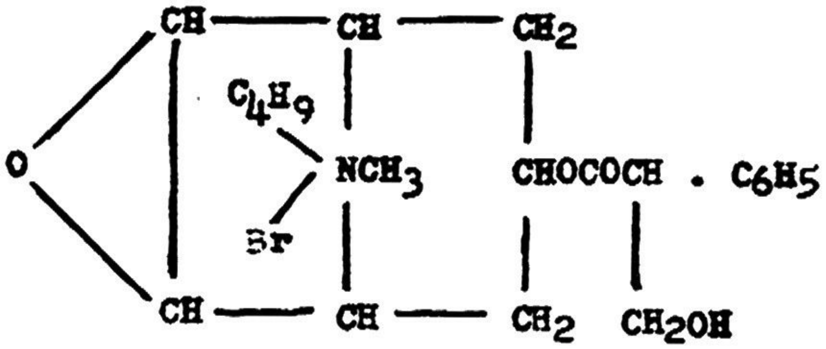
United States Patent 2,305,460 Scheuing (Plaintiff's Ex. 23, Tr. 107)

German Patent 145,996 Merck (Plaintiff's Ex. 22, Tr. 102)

The applicant appealed to the Board of Appeals, which affirmed the Examiner (Tr. 81). Action was then filed in the District Court, which dismissed the complaint, holding the claims to be unpatentable (Tr. 57). From that judgment, plaintiff took an appeal *only as to claim 10,* a claim to the product. Other claims denied by the District Court, directed to the method of making the compound, are not involved in this appeal.

The compound of the present invention is claimed as follows:

10. As a new product quaternary scopolamine-bromobutylate having a melting point of about 142° to 144° C having the following structural formula:—



This compound is being sold commercially in Europe in very substantial quantities (Tr. 12) by plaintiff under the trade-mark "Buscopan", as which it will be hereinafter referred to.

Buscopan is a valuable pharmaceutical product for the relief of a muscular spasm (Tr. 12; plaintiff's Exhibits 11, 13, Tr. 96, 97), principally to relieve pain, but also as an aid in X-ray work. It has been found very useful in relaxing cramps caused by ulcerous conditions of the stomach (Tr. 12, plaintiff's Exhibit 11, Tr. 96); in relieving contractions of the intestines and the urinary tract (Tr. 12); in shortening labor (Tr. 12, plaintiff's Exhibit 10, Tr. 96); in aiding X-ray diagnosis by removing spasmic conditions (plaintiff's Exhibit 20, Tr. 100); and for other similar purposes.

Buscopan is a derivative of scopolamine, and is closely related to atropine, both of which have spasmolytic effects. It is a homolog of scopolamine bromomethylate* (FF. 12, Tr. 55), which has also been sold as a spasmolytic under the trademark "Pamine" (Tr. 12).

Buscopan, however, has very unexpected and advantageous properties, as compared with scopolamine, atropine or Pamine (FF 11, Tr. 55), in that it has substantially the same spasmolytic effectiveness, yet is almost free of the annoying or even toxic side-effects which are produced by the other compounds (Tr. 15, plaintiff's Exhibit 4, Tr. 90). It can therefore be given in much larger doses (Tr. 37), without danger to the patient, and in such doses is effective in many serious conditions where the smaller quantities of the other compounds, the largest doses which could safely be given, would be entirely inadequate.

---

* Disclosed in the German Merck patent relied on as prior art by the District Court.

More specifically, Pamine, as well as scopolamine, have very disturbing side effects, which can be toxic (Tr. 13-15, plaintiff's Exhibit 5, Tr. 91). The best known of these effects is the dilatation of the pupil of the eye, which can last for hours or even days, which requires the wearing of dark glasses and prevents reading. In addition, these compounds seriously inhibit the excretion of saliva, which results in dryness of the mouth and considerable discomfort. Finally, such materials are likely to stimulate the heart rate to a degree which is alarming and painful, and at times even dangerous.

Buscopan has none of these side effects, or, if it has them at all, they are present to such a slight degree as to be negligible.

The District Court, in its decision relied solely on the German patent to Merck (plaintiff's Exhibit 22, Tr. 102). This patent discloses specifically only the methyl and ethyl bromides of scopolamine. This patent mentions "alkyl bromides",* in the sense of the methyl and ethyl bromides.

## STATUTES INVOLVED

The statutes involved in this case are 35 U.S.C. § 102(a), 102(b) and 103, (Patent Act of July 19, 1952, Public Law 593, 82nd Cong. 2nd Session) which read as follows:

> "§ 102. Conditions for patentability; novelty and loss of right to patent

---

* Ethyl, methyl and butyl are all "alkyl" radicals.

> A person shall be entitled to a patent *unless*—[*]
>
> (a) the invention was known or used by others in this country or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or".
>
> "§ 103. Conditions for patentability, non-obvious subject matter
>
> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

## STATEMENT OF POINTS

The points involved in this appeal are:

1. That the District Court erred as a matter of law in refusing to allow claim 10, despite

(a) failure to find the subject matter thereof disclosed in the prior art; and

(b) a positive finding that the product of this claim had unexpected properties.

2. That the District Court erred in holding *in effect* that Merck shows that bromides of all alkyl derivatives of scopolamine are advantageous, whereas in fact the teaching of Merck is limited to methyl and ethyl compounds.

3. That the District Court erred as a matter of fact and as a matter of law in holding that the product of claim 10

---

[*] Emphasis added.

does not possess new and unexpected properties sufficient to impart patentability; whereas the evidence clearly showed it to possess such properties.

4. The District Court erred in dismissing the complaint as to claim 10.

## SUMMARY OF ARGUMENT

The statute provides that an applicant shall be entitled to a patent *unless* either:

(a) the invention is previously patented or described in a prior printed publication; or

(b) the differences between the invention and the prior art would have been obvious to a person skilled in the art.

Neither of these conditions is met here because:

(a) the Merck German patent discloses only the methyl and ethyl scopolamine bromides, *not* butyl scopolamine bromide;

(b) butyl scopolamine bromide has, *as the District Court found,* unexpected and unusual advantages, and was therefore not obvious to a person skilled in the art.

The rule is that homologs of known compounds are not patentable *unless* they possess unexpectedly advantageous properties; since they would be expected to have properties similar to the known compounds. But, when they have unobvious properties, they are patentable.

The mere naming of scopolamine bromomethylate in the German patent implies the possible existence of a whole series of scopolamine bromoalkylates. This is true in every case involving homologs, since the alkyl series is far the most wide-spread group of organic radicals. Also, other homologs of the series can ordinarily be made by the same procedure as the methyl compound, with certain changes which are usually obvious to any skilled chemist.

Nevertheless, new homologs of a known compound are patentable *if* they have new and unobvious properties, even though they could readily be produced by a chemist, once their desirability is known.

The real invention in this type of case lies in the discovery of the unobvious utility of the homolog. Millions of chemical compounds can be conceived or even produced, but there is no patentable invention in a chemical compound *merely* because it is novel unless it is also *useful*. Since the homolog of a known compound would be expected to have substantially the same properties as the prior substances, the proof of substantially different and advantageous properties confer on it the quality of invention.

Reference in the Merck patent to "alkyl" groups is not intended to refer to the class of alkyl radicals broadly, but merely to methyl and ethyl.

The Merck German patent must be strictly construed, and can be relied on only for what is clearly disclosed in it, not for what can be conjured out of it in the light of applicant's teaching.

Appellant has made an important contribution to medical progress, and its compound enjoys substantial commercial success. It should not be deprived of protection thereon, and in fact the statute requires, on the facts found by the District Court, that a patent should be granted to it.

## ARGUMENT

### 1. LEGAL QUESTION INVOLVED

The statutes, 35 U.S.C. 102, 103, state that an applicant is entitled to a patent *unless* either:

(a) the matter claimed is disclosed in the prior art; or

(b) it would have been obvious, from the prior art, to a person skilled in the art.

The subject matter of the claim in issue here, scopolamine bromobutylate*, is plainly not disclosed in the German patent to Merck, which shows only the bromomethylate and the bromoethylate (FF 6, Tr. 55). Therefore the first condition of the statute is not met.

The question then is whether the bromobutylate would be obvious to one skilled in the art from the disclosure of the Merck patent.

### 2. MERCK, AS A FOREIGN PATENT MUST BE STRICTLY CONSTRUED

Let us remember at the outset that, as this Court said in *Becket* v. *Coe,* 98 F. 2d 332; 69 App. D.C. 53, a foreign patent should be used as a reference only for what is clearly and precisely disclosed in it, and not for what can be made out of it.

The Court there said:

> "Foreign patents are valid references when there is a clear disclosure of the invention sought to be patented in the United States. In re Cross, Cust. & Pat. App., 1932, 62 F. 2d 182. But when such a patent merely prophesies what can be done without setting forth that it has been done, or makes claims for things not fairly disclosed in the specification, the foreign patent does not anticipate. Westinghouse Air-Brake Co. v. Great Northern Ry. Co., 2 Cir., 1898, 88 F. 258; General Electric Co. v. Hoskins Mfg. Co., 7 Cir., 1915, 224 F. 464; Haynes Stellite Co. v. Chesterfield, supra; American Stainless Steel Co. v. Ludlum Steel Co., 2 Cir., 1923, 290 F. 103. This court has said, in Davies v. Coe, 1936, 65 App. D.C. 345, 346, 83 F. 2d 602, 603:
>
> 'The disclosure of a foreign patent is to be measured not by what may be made out of it, but what is clearly and definitely expressed in it. In re Elk, 57 App. D.C. 203, 19 F. 2d 677; Carson v. American Smelting & Refining Co. (C.C.A.) 4 F. 2d 463.'

---

* Also called butyl scopolamine bromide.

And in the Westinghouse Case the court held valid a United States patent for an air-brake, despite a prior English patent which stated: 'It is obvious that it (the stem of the emergency valve) might be worked as described by a separate piston in a cylindrical cavity communicating on the one side with the auxiliary reservoir, and on the other side with the train pipe.' In answering the contention that this described the valve set forth in the United States patent, and that therefore the latter lacked invention, the court said:

> 'The prophetical suggestions in English patents of what can be done, when no one has ever tested by actual and hard experience and under the stress of competition the truth of these suggestions, or the practical difficulties in the way of their accomplishment, or even whether the suggestions are feasible, do not carry conviction of the truth of these frequent and vague statements. The nature and character of the invention of 376,837 were, in the record heretofore before this court, put to rigorous tests by examination and cross-examination in court; and the result which was then reached is not shaken by merely a single sentence in the English patent.' (88 F. at page 263)

Much the same thought is expressed in American Stainless Steel Co. v. Ludlum Steel Co., supra:

> '. . . it requires more than prophecy of what may be done, or than declaration of what ought to be accomplished, to make a good patent reference, not to speak of an anticipation. It is necessary to show with reasonable certainty how the desired result can be accomplished.' (290 F. at page 106)

### 3. HOMOLOGS OF KNOWN COMPOUNDS ARE PATENTABLE IF THEY HAVE UNOBVIOUS PROPERTIES

Second, it is admitted that scopolamine bromobutylate is a homolog of the compounds disclosed in Merck. Homologs are compounds which differ in the presence of a number of methyl or $CH_2$ groups. The commonest homologous series is the alcohols:

| | |
|---|---|
| $CH_3OH$ | Methyl alcohol |
| $+ CH_2$ | |
| $C_2H_5OH$ | Ethyl alcohol |
| $+ CH_2$ | |
| $C_3H_7OH$ | Propyl alcohol |
| $+ CH_2$ | |
| $C_4H_9OH$ | Butyl alchohol |
| etc. | |

The radicals

$CH_3$—methyl $C_2H_5$—ethyl

$C_3H_7$—propyl $C_4H_9$—butyl

are known as the alkyl radicals.

Buscopan is an alkyl bromide of scopolamine; so is the Pamine of the Merck patent. Therefore these compounds are homologs, the remainder of their chemical composition being identical.

Homologs ordinarily have very similar properties, and can usually be prepared by similar procedures, with certain changes in times and temperatures known to any skilled chemist. Therefore it is ordinarily held that one homolog is not patentable over another, where the new has no unexpected and unobvious properties as compared with the old. This has been stated on a number of occasions, namely *in re Hass,* 141 F. 2d 122, 125, where the Court of Customs and Patent Appeals held that:

> "We are of opinion that the tribunals of the Patent Office were right in holding that, in order to be patentable, novel members of a homologous series of chemical compounds must possess some unobvious or unexpected beneficial properties not possessed by a homologous compound disclosed in the prior art."

But this rule does not apply where the new homolog has new and unexpected advantages. For example, in

*Ruskin* v. *Watson,* 123 F. Supp 33, the District Court of this Circuit recognized patentability in a compound which the Patent Office claimed to be a homolog of a known compound because, regardless of whether it was a homolog or not, it possessed such unobvious advantages as to be patentable. The decision reads as follows (page 34):

> "Assuming, without deciding, that nikethamide adenylate and nicotinamide adenylate are homologous compounds, a presumption of unpatentability arises, and the burden is on the plaintiff to rebut that presumption by a showing that nikethamide adenylate possesses unobvious or unexpected beneficial properties, not actually possessed by nicotinamide adenylate.
>
> "The question presented here is whether or not nikethamide adenylate has been shown to have unexpected and unobvious properties not possessed by nicotinamide adenylate. The uncontradicted testimony was to the effect that Dr. Ruskin had several cases in which he had used nicotinamide adenylate and nikethamide adenylate. These cases involved muscular spasm, such as bursitis, ear noises and itching. In every case, after failure of the nicotinamide adenylate to give relief, nikethamide adenylate was effective. I find, therefore, that nikethamide adenylate has properties of a far different character than from those of nicotinamide adenylate; that is, that nikethamide adenylate possesses unobvious and unexpected beneficial properties, not actually possessed by nicotinamide adenylate.
>
> "It is true that both nicotinamide and nikethamide have been used to some extent in the treatment for heart disease of various types. Both are of some effect in treating pellagra, although nikethamide alone is undesirable because of the high dosages required. Dr. Ruskin testified that nikethamide in high dosages caused convulsions.
>
> "I find that this is not a case of double patenting and that nikethamide adenylate is patentably distinct from nicotinamide adenylate."

Likewise, in *Sterling Drug Inc.* v. *Watson,* 135 F. Supp. 173, 176 Judge Morris, in allowing a patent, stated:

> "And there can hardly be any serious question that these beneficial characteristics were both unexpected and unobvious, which is the test to be applied in the matter of the patentability of a compound that is a homologue of another."

This Court, in a case involving an alloy the ranges of ingredients of which lay within broader ranges of the prior art, but which had advantageous properties not taught by the prior art, recognized the presence of invention (Becket v. Coe, supra).

That situation is quite analogous to the present one. The disclosure of any alkyl compound presupposes the possible existence of a range or series of alkyl compounds differing by $(CH_2)_n$ (where n can be any whole number) from the compound disclosed. But within this range or series one or more particular members may be patentable if they have properties unobvious to a person skilled in the art.

The true invention in these cases is in the discovery of the unobvious properties of the new compound. The mere discovery of a new compound, absent any utility for it, does not constitute invention.

In *Smith, Kline & French Laboratories* v. *Clark & Clark,* 62 F. Supp. 971 (affirmed at 157 F. 2d 725), at page 993, the rule is stated as follows:

> "It is is the effect it produces which brings the composition up to the high standard of invention in therapeutics. Without the useful effect, the composition, although new, is of no value, except possibly academically, and certainly unpatentable. The field of chemistry is filled with formulas and compositions for which no use has yet been found. Are we to discourage the finding of beneficial uses of known formulas and compositions by concluding that the publication of the

> laboratory method of preparing compositions without declaration of purposes precludes any further findings with regard to that substance from being the subject of a patent? If we were to so conclude, we should deprive the protection of our patent law to the fields of chemistry and therapeutics, fields in which great advances have been made towards the relief of the suffering of mankind and aiding man to a longer and a better life."

The same thought has been expressed by the Board of Appeals of the Patent Office (Ex parte Buc et al, 114 U.S.P.Q. 552, 553) as follows:

> "Utility of a compound is an essential part of an invention directed thereto and by statutory provision a patent cannot be granted unless the compound does have a utility which is either obvious or is established by proper tests."

And, in the application of Henze, the Court of Customs and Patent Appeals says (181 F. 2d 196, 202):

> "To those skilled in the chemical art, one homologue is not such an 'advance' over an adjacent member of the series as requires invention, unless the beneficial properties realized in the new homologue lie clearly outside of the expectations which knowledge of his science would inform the trained chemist should be inherent in the product. See Ellis on Patent Claims, Sections 474, 475. In the latter event, it may be possible to say that inventive genius and not mere skill of the calling was required to select the new compound, otherwise not."

Nor does the fact that a skilled chemist could make the compound, once it and its advantages are disclosed, render it unpatentable, even though the process for making it might be unpatentable. Most inventions can be reproduced, once their nature is taught.

This is clearly stated in *Smith, Kline & French* v. *Clark & Clark,* supra, at page 976, which reads:

> "A skilled chemist, following Edeleano's methods as described in his paper and applying the knowledge of his profession and of the art prior to Alles, might very well be able to produce salt of 1-phenyl-2-aminopropane, but not a substance having the effects of the Alles' compound for therapeutic purposes. To prepare such a substance requires original experimentation on the part of the chemists as to effect of the substance upon animals and man. Edeleano's disclosure taught only the manner by which the base of the compound could be prepared and referred incidentally to two salts thereof without further identification. It is insufficient as an anticipation of a disclosure of effect and therapeutic usefulness of a certain salt of the base."

In *ex parte Dettwyler,* 65 USPQ 288, the Board of Appeals of the Patent Office held an isomer of an old compound to be patentable because of an unexpected difference in effect, although it states that "as a rule, isomers of old compounds are not regarded as patentable". The decision also states that in the production of the compound the "two intermediates are condensed in the usual manner". Here then is a holding that an isomer (which is normally unpatentable for the same reasons as a homolog) may be patentable even though it is an isomer of a known compound and the method of making it is old.

Attention is also directed to the decision in *ex parte Burtner and Arbit,* 89 USPQ 547. In that case, at page 549, the Board of Appeals says:

> "As pointed out by appellants, it is well settled that a new compound may be patentable despite the fact that its mode of preparation would be apparent from its structural formula. The criteria for determining patentability of chemical compounds are quite different from those applicable to processes."

### 4. BUSCOPAN HAS UNOBVIOUS PROPERTIES

The evidence in this case clearly shows, and in fact the District Court found (FF 11, Tr. 56), that Buscopan has unexpected properties. It follows that this compound was not obvious to persons skilled in the art, and is patentable.

Dr. Wick's evidence, as well as the descriptions of the properties of Buscopan, as compared with Pamine or with scopolamine hydrobromide, contained in Plaintiff's Exhibits 7 to 20, (Tr. 94-100) clearly show these unobvious properties. The testimony is summarized by Plaintiff's Exhibit 22, (Tr. 101) which shows:

1. That, whereas Pamine is 3.6 times as active as atropine* in the inhibition of saliva, Buscopan is only one-twentieth (5-100ths) as active. The ratio of activity is 70 to 1.

2. Wheeras Pamine is 4 times as active as atropine in producing cardiac acceleration, Buscopan is only one-thirtieth (33-1000ths) as active. The ratio is 120 to 1.

3. Whereas Pamine is 3 times as active as atropine in producing dilatation of the eye, Buscopan is only one-five hundredth (2-1000ths) as active. The ratio is 1500 to 1.

4. Buscopan is almost as active in spasmolysis as Pamine; it can be given in much larger doses, and therefore is much more effective as a spasmolytic. (Tr. 37)

Surely these differences in action between Buscopan and Pamine would not "be obvious to one skilled in the art" (35 U.S.C. 103). In fact, the District Court found specifically that Buscopan has "an *unexpected* degree of freedom from undesirable side effects". (FF 11, Tr. 55) (Emphasis supplied) And this unobviousness is fortified by the fact that, whereas butyl atropine is *more* toxic than atropine (Tr. 35), butyl scopolamine bromide is *so much less* toxic than either scopolamine hydrobromide (the compound in which substitution of a butyl radical for hydrogen produces Buscopan) or methyl scopolamine bromide (Pamine) that its toxic effects are almost negligible. (Tr. 22; Plaintiff's Exhibit 8, Tr. 95).

---

* It is conventional to refer to atropine as a standard in evaluating compounds of this general type (R, p. 68).

### 5. THE DISTRICT COURT MISCONSTRUED MERCK

The District Court, in finding 6 (Tr. 55), says that Merck "states that bromides of alkyl derivatives of scopolamine" have greatly diminished side effects. In this statement, the Court misconstrues the patent (Ex. 23, Tr. 102).

The German patent refers in the first paragraph, to "the salts of methyl and ethyl atropine". The second paragraph says that "bromides of similar derivatives of other alkaloids of the . . . scopoleine group has furthermore shown that said compounds are favorably distinguished also over the original alkaloids since they are entirely free of undesired side-effects or since such side effects at least strongly recede".

The next paragraph refers to the production of "Said bromides" from "the corresponding alkyl bromides" by bringing the alkaloid together with "said alkyl bromides".

These are the *only* points at which the word "alkyl" is used in the Merck patent. Significantly, the *claim* specifically limits itself to the bromomethylates and bromoethylates.

Thus there is no teaching in Merck that the bromobutylate when used as a spasmolytic would have the almost complete freedom from undesirable side effects which were discovered by the applicant.

### 6. MERCK'S STATEMENTS ARE INACCURATE

Further, the statement in the patent to Merck that methyl and ethyl scopolamine bromide have less side-effects than scopolamine is clearly contradicted, not only by Dr. Wick's testimony as summarized in Plaintiff's Exhibit 22 (Tr. 101), but also by the publications in the field, such as Plaintiff's Exhibit 6 (Tr. 92). In other words, when the physicians came to evaluate Pamine, tests showed that it actually had much worse side effects than scopolamine hydrobromide or atropine. Surely no one skilled in the art would conclude from this that the *butyl* bromide, Buscopan, would have substantially the same spasmolytic activity as atropine but would, at the same time, be *in fact* substantially non-toxic.

### 7. CONCLUSION

It is then clear that there is no true teaching in the art of the advantages of Buscopan, which, as the District Court found, were *unexpected* or unobvious.

The Court found that Buscopan has great utility and unexpected properties. The product has had substantial commercial success, sales in Germany alone amount to over 1,000,000 packages a year. It is also sold in other European countries. There is every reason, then, to say that this new product with its unexpected advantages should not be refused protection.

Appellant therefore submits that the judgment of the District Court dismissing the complaint as to claim 10 is erroneous and should be reversed.

Respectfully submitted,

JENNINGS BAILEY, JR.
*Attorney for Appellant*

# APPENDIX

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# JOINT APPENDIX

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172 Filed July 13, 1955

IN THE DISTRICT COURT OF THE UNITED STATES
FOR THE DISTRICT OF COLUMBIA

Civil Action No. 3069-'55

C. H. BOEHRINGER SOHN, a Partnership, Ingelheim am Rhein, Germany, *Plaintiff*,

v.

ROBERT C. WATSON, Commissioner of Patents, United States Patent Office, Washington, D. C., *Defendant*.

## Complaint to Authorize the Commissioner of Patents to Issue Letters Patent

### I.

This action arises under Section 145 of the Patent Act of 1952 (U. S. Code, Title 35, Section 145).

### II.

Plaintiff, C. H. Boehringer Sohn, is a partnership consisting of Albert Boehringer, Ernst Boehringer, Ilse Liebrecht, born Boehringer, and Julius Liebrecht, all citizens of Germany, and has an office and place of business at Ingelheim am Rhein, Germany. Plaintiff is the assignee by assignment dated October 8, 1951 (and recorded in the United States Patent Office on August 17, 1951, Liber 0229, page 538) from Franz Adickes, of Ingelheim, Germany, of the entire right, title and interest in and to the invention disclosed in an application for United States Letters Patent executed by said Franz Adickes as inventor concurrently with said assignment, and filed in the United States Patent Office on October 17, 1951 under Serial No. 251,840.

173 III.

Defendant, Robert C. Watson, is Commissioner of Patents of the United States, is a citizen of the United States, has his official residence as Commissioner of Patents in the District of Columbia, and is made defendant in this Complaint in his official capacity as Commissioner of Patents of the United States.

IV.

The invention disclosed in said application, Serial No. 251,840, and assigned to plaintiff, as aforesaid, comprises certain new and useful improvements in process for the production of scopolamine-bromobutylate, not known or used by others in this country before the invention or discovery thereof by said Franz Adickes, and not patented or described in any printed publication in this or any foreign country before his invention or discovery thereof or more than one year prior to this application, and not in public use or on sale in this country for more than one year prior to his application, and not abandoned to the public and not disclosed in any application for any foreign patent filed more than twelve months prior to said application for patent in the United States. Said application, as filed in the United States Patent Office complied in all respects with the requirements of the law in such case made and provided.

V.

Said application for United States Letters Patent was duly prosecured in the United States Patent Office, and claims 5 through 10 inclusive, 12 and 13, which were presented therein, and which were in proper form and
174 substance, were finally and erroneously rejected by the Primary Examiner in said Patent Office.

VI.

Plaintiff, in due compliance with the law, appealed from said final rejection to the Board of Appeals in the United

States Patent Office, and said Board of Appeals, after hearing said appeal, erroneously affirmed the final rejection of said claims by said Primary Examiner in a decision rendered on May 17, 1955.

### VII.

No appeal has been taken from the said decision or from any decision of the Board of Appeals to the United States Court of Customs and Patent Appeals, and no such appeal is pending or has been decided.

WHEREFORE, plaintiff brings this Complaint and prays for a decree adjudging that it is entitled to receive a patent for said invention and authorizing the Commissioner of Patents to issue a patent of the United States upon said application Serial No. 251,840 for the said invention defined in said claims 5 through 10 inclusive, 12 and 13.

C. H. BOEHRINGER SOHN

By JENNINGS BAILEY, JR.
*Attorney for Plaintiff*

Jennings Bailey, Jr.
1317 F Street, N. W.
Washington 4, D. C.

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175 Filed July 22, 1955

### Answer to Complaint

To the Honorable the Judges of the United States District Court for the District of Columbia.

I, II, III. The defendant admits the allegations of paragraphs I, II, and III of the complaint.

IV. He denies the allegations of the first sentence of paragraph IV and admits the allegations of the second sentence of that paragraph.

V. He admits that the plaintiff's application was duly prosecuted as alleged in paragraph V. He denies that the claims referred to in that paragraph were proper in form and substance and denies that their rejection was erroneous.

176 VI. He denies that the action of the Board of Appeals referred to in paragraph VI was erroneous. He admits the remaining allegations of that paragraph.

VII. He admits the allegations of paragraph VII.

FURTHER ANSWERING, defendant states that the plaintiff is not entitled to a patent containing any of the claims referred to in the complaint for the reasons given and in view of the references cited in the Examiner's statement and the decision of the Board of Appeals in the application here involved. Profert of copies of the said statement, decision, and references is hereby made.

Respectfully submitted,

E. L. REYNOLDS
*Solicitor, U. S. Patent Office,*
*Attorney for Defendant.*

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## EXCERPTS FROM TRANSCRIPT OF TESTIMONY

22 Thereupon,

**Helmut Wick**

was called as a witness by and on behalf of the Plaintiff, and, being first duly sworn, was examined, and testified as follows:

Direct Examination

By Mr. Bailey:

Q. Will you state your name, age and residence? A. My name is Doctor Helmut Wick.
Q. Your age? A. 45.
Q. Your residence? A. Ingleheim-on-the-Rhine.

Q. That is in West Germany? A. Yes.

Q. What is your occupation? A. I am a pharmacologist at C. H. Boehringer and Company.

Q. That is the plaintiff in this case? A. Yes.

Q. What is the business of C. H. Boehringer? A. He has a pharmaceutical house, and produces chemical products.

23 Q. What was your education? A. I went through high school and studied medicine, made my examinations in 1937.

Q. Did you receive a degree of M.D.? A. Yes. I am an M.D., Doctor of Medicine.

Q. At what universities did you study? A. I studied at the University of Heidleberg, Berlin, Vienna, Munich, Frankfurt and Marburg.

Q. How long have you been with Boehringer? A. Since the end of 1947.

Q. What have your duties been there? A. To try new compounds which the chemists have synthesized for possible therapeutic value.

Q. What particular types of compounds have you worked on? A. In the first years on spasmolytic drugs.

Q. By that you mean drugs which relieve spasms or cramps? A. Yes.

Q. Do you know Franz Adickes, the inventor of this— A. Yes. I know him perfectly well.

Q. Is he an employee of Boehringer? A. Yes, he is.

Mr. Bailey: I offer in evidence as Plaintiff's
24 Exhibit 1 a certified copy of the file wrapper and
contents of the application in suit here, Serial Number 251840, filed October 17, 1951.

That is the complete file.

The Court: No objection?

Mr. Schimmel: No objection.

The Court: Received as Plaintiff's Exhibit Number 1.

(Plaintiff's Exhibit 1 was received in evidence.)

By Mr. Bailey:

Q. Are you familiar with the subject matter in the suit? A. Yes.

Q. What is that subject matter? A. Buscopan.

Q. What is its chemical name? A. The chemical name of this compound is scopolamine bromo-butylate.

Q. When you call it buscopan, is that Boehringer's trade name for it? A. Yes.

Q. Has it also been called occasionally SKAF 1637? A. Yes; only for investigational purposes in this
25 country.

Q. Is buscopan sold by the plaintiff? A. Beg pardon?

Q. Does the plaintiff sell buscopan? A. Yes.

Q. I hand you a pamphlet in German, entitled "The Pharmacological Basis of Therapeutics", and ask you if you identify that. A. Yes, sir.

Q. What is that? A. That is a pamphlet describing the usefulness of the product buscopan in the treatment of ulcers.

Q. By whom is it published? A. By our pharmaceutical house.

Mr. Bailey: Mr. Schimmel, I have no photostats of these, nor translations. They are merely offered to show that the product is being actively promoted by the plaintiff.

Mr. Schimmel: May I ask what the date is?

Mr. Bailey: Very well.

By Mr. Bailey:

Q. Do you know what the date of this is? A. No.

Q. You have no idea how long it has been published? A. No.

26 Mr. Schimmel: I am asking for the date, Your Honor, for this reason: That it seems to me material subsequent to the filing of the application in connection with this question of utility was mentioned by Mr. Bailey and which is raised in the decision must be related

to the date of the application because of the fact the statute requires every applicant to describe the utility of his particular compound and it must be the utility at that particular time or prior to the time when he filed the application.

If there is no utility at that time there is no basis for a patent.

Utility developed subsequently which may show advantage of the product is immaterial to this question. That should not be considered on the question of patentability. I think that date factor is important in this situation.

The Court: Are you going to be able to supply the date, Mr. Bailey?

Mr. Bailey: I can't supply the date, but I am reasonably certain that the date is later than the filing date of the application.

The Court: What do you say to the principle?

Mr. Bailey: I say that Mr. Schimmel is completely wrong. In the first place, the application discloses that scopolamine bromo-butylate has a very extraordinary importance as a spasmolytic. It is useful here as a spasmolytic.

27 That is why it is useful in ulcers. We have disclosed its utility in the application. I submit that we are not restricted to the tests that were carried out prior to the filing of the application in order to demonstrate utility. We could make tests today to demonstrate utility. The decisions, one after another, say a man is entitled to all the uses to which his invention may be put. If he made an invention it may have advantages he did not appreciate at the time and yet in his patent he is entitled to the benefit of those advantages, and I think that here we are proving that the material has utility.

Now, the question is not, did the applicant prove conclusively before he filed his application that the material had utility. I think the question before Your Honor is, was he right when he said the material had utility.

Your Honor, a man can file an application on a device that he has never tested at all. He doesn't have to have actually made and constructed a device in order to get a patent on it. A man can take a drawing of a machine.

The Court: Let me ask Mr. Schimmel: As I understand this proceeding, it is de novo.

Mr. Schimmel: It is de novo, but just the same, before the patent can be granted it is based on the application that was presented to the Patent Office. The reason I
28 raise this, Your Honor: If you will refer to the decision of the Board of Appeals in this case, which is in the folder—on page 7 of that decision, that is Item D in the folder, you, I think, will get a view of how this question arose. In the first full paragraph the decision of the Board of Appeals mentions a second Wick affidavit and describes the results in the quoted paragraph toward the bottom of the page of the spasmolytic effects of the scopolamine bromo butylate. This is the important thing, it seems to me:

"We are unable to reconcile the last quoted portion with the statement in the original specification, to the effect that the scopolamine bromo butylate is about equal to atropine in this effect."

In other words, we have inconsistent statements: One in the specification as to the utility of the compound for this purpose, and another produced in the affidavit as evidentiary of its utility, which was contrary to the statement of the original specification.

Now, in that situation the Board of Appeals says we are in a dilemma. What is this utility? Is there any utility at all which the statute requires contrary to what Mr. Bailey says, which the statute requires as a prerequisite to the granting of a patent.

There must be a utility disclosed, and I am ready
29 to support that by many cases.

The Court: We had a demonstration here in a case you had—

Mr. Schimmel: It was to show—

The Court: You say this application does not make claim for utility?

Mr. Schimmel: No, I don't say this. The application, I admit, says it is useful as a spasmolytic, and it compares its utility with atropine, and it says it is about equal to atropine. During the prosecution of the case, affidavits were submitted which made entirely different statements which said, according to the quoted portion which the Board has in its decision, which says it is one/hundredth to two one-thousandths as powerful as atropine in that particular field.

Is the statement of utility under those circumstances in the application correct or is it incorrect?

The Court: Let's assume that they didn't show it before the Patent Office. You say they can't show it here?

Mr. Schimmel: I say with respect to that particular application, which is in a foreign language, which has no date on it, we don't know whether it is related to this specific utility disclosed in the application or not.

The Court: That is a different thing.

Mr. Schimmel: I was going to raise that.

The Court: That is, the probative value of it?

Mr. Schimmel: I would like to know first, is that publication with relation to this specific utility?

Mr. Bailey: May I ask the witness two questions?

Mr. Schimmel: Before we could get that we ought to have a translation of it before it is admitted in evidence.

The Court: It won't do me any good unless you do translate it.

Mr. Bailey: As I say, I am offering it merely as showing—I will let the doctor testify as to the facts of the statements and will skip this.

Before I leave that, Your Honor, I would like to overcome a possible misconstruction on this matter that Mr. Schimmel seems to have in mind.

The application says that the action on the stomach gut and gall bladder is about equal to that of atropine, and the far-reaching non-toxicity, scopolamine-bromobutylate has a very extraordinary importance as a spasmolytic.

The important affidavit that the Board read is not complete. It says: "... scopolamine-bromobutylate is only from 1/100 to 2/1000 as powerful as atropine in the tested spasmolytic effect, according to the Nyman tests ..."

31 Doctor Wick's evidence will show that, according to certain tests of an isolated piece of intestine which is activated or stimulated by acetylcholine, and that is just a test of a piece of gut taken out of an animal, and you stimulate it artifically and you test the spasmolytic effect of various materials on it, that in that test buscopan has only a very small fraction of atropine.

The publications of these doctors that we will bring in to Your Honor, and Doctor Wick's own animal test will prove that in so far as activity in the human body is concerned, which is what is important, and that is what the specification says, the gut, gall bladder, stomach, that actually it is substantially of the same activity as atropine and without all the side effects of atropine.

In other words, this was one test actually, if this test had never been mentioned, probably, but it is a test, meaningless so far as pharmaceutical value is concerned, where he says this so-called inconsistency is.

By Mr. Bailey:

Q. In what form does Boehringer sell buscopan? A. It sells buscopan in the form of sugar-coated tablets and in the form of solution for injection.

Q. Do you have any samples of buscopan? A. Yes; in my briefcase.

32 Q. Is this such a sample? A. Yes.

Mr. Bailey: I offer in evidence as Plaintiff's Exhibit Number 2 the box of tablets of buscopan.

Mr. Schimmel: No objection.

The Court: Received.

(Plaintiff's Exhibit 2 was received in evidence.)

By Mr. Bailey:

Q. What is the amount of buscopan in each of those tablets? A. 10 milligrams in each.

Q. What is the recommended administration? A. Three times daily; one or two tablets.

Q. That is from 30 to 60 milligrams a day; is that correct? A. Yes.

Q. How much is a milligram? A. A milligram is a thousandth part of a gram.

Q. As compared with atropine, what is the ordinarily accepted maximum daily dose of atropine? A. Half a milligram.

Q. Doctor, I hand you some pages from a book by Goodman and Gilman, "The Pharmacological Basis of
33 Therapeutics", these being copies of page 542, 552,
559 and 560, and ask you if you find in there any indication as to the dosages—

Mr. Bailey: I will offer this, first, in evidence as Plaintiff's Exhibit 3.

Mr. Schimmel: No objection.

The Court: Received.

(Plaintiff's Exhibit 3 was received in evidence.)

By Mr. Bailey:

Q. Do you find in there any indication of the allowable dosage of atropine? A. Yes.

Q. Where do you find it? A. I find it on page 552 in Table 27.

Q. What does that indicate as far as administration of one milligram of atropine is concerned? A. That means after the administration of one milligram of atropine that is caused definite dryness of the mouth, slowing of the heart rate, followed by some acceleration, mild dilatation of the pupils.

Q. Now, in so far as the pamine, the material of the Merck patent, is concerned, do you find any such description of that in this book? A. Yes.

34 Q. Where do you find that? A. We find it on page 559, lower right.

Q. What does that state as to the average daily dose? A. It states that the average adult dose is 2.5 milligrams three times daily, before meals; that the pharmacological properties of this compound are typical of anticholinergic atropine-like drugs.

Q. Doctor, what are the approximate sales of buscopan by the plaintiff? A. In Germany, more than one hundred thousand packages per month. More than one hundred thousand packages per month.

Q. Is it sold in any other countries? A. In England and France.

Q. Are there any other countries? A. It is sold in Italy and in Spain.

Q. For what purposes is it sold? A. It is sold primarily against ulcers of the stomach and of the duodenum, and against cramps of the intestine, cramps or spasms in the bile duct and the gall bladder, of the urinary tract and for shortening labor.

Q. Is that for use in treatment of human beings? A. Yes.

35 Q. What products have been previously used for similar purposes? A. Atropine and their synthetic derivatives.

Q. Was scopolamine also sold to some extent? A. But only to a small extent.

Q. When you mentioned derivatives, do you include pamine? A. No. In our country it has not been used for this purpose. Other derivatives—

Q. Has pamine been sold for similar purposes? A. Yes.

Q. In the United States? A. Yes.

Q. Now, pamine is scopolamine bromobutylate; is that correct? A. Yes.

Q. Is that also known as pamine bromide? A. Yes.

Q. And epoxymethamine bromide? A. Yes.

Q. Doctor, in your affidavit which was filed in this case in the Patent Office, you make the statement:

"Scopolamine bromobutylate is only from one/hundredth to 2/1000th as powerful as atropine in the tested spasmolytic effect according to the Nyman Test."

36 Now, to what type of test did that refer? A. Our experiments.

Q. When you say the bromobutylate is only 1/100th to 2/1000th as powerful as atropine. A. In those tests where the pieces of gut are stimulated to contraction by acetycholine. Under these conditions buscopan has only 1/100th or less activity as atropine.

The Court: Has what?

Mr. Bailey: 1/100th or less the effect of atropine.

The Witness: If one uses another compound for stimulating the intestine—for instance, pilocarpine—well, it is practically as powerful in relieving spasms as atropine.

By Mr. Bailey:

Q. Is buscopan as effective as atropine in relieving cramps in the human body? A. Yes. Practically in the same dose.

Q. Is that based on your own test, that statement? A. To some extent; yes. And to another extent, clinically.

Q. You mean that you have had clinical reports from others? A. Yes.

Q. And have there been a number of publications describing the effectiveness of buscopan in relieving cramps of various sorts and spasms? A. Yes. 37

Q. To your knowledge, how many such publications have there been? A. Dealing with this field I think must be around one hundred.

Q. Have they been publications in accepted medical journals? A. Yes.

Q. By physicians? A. By physicians or the leading men; yes; the university clinics.

Q. What are the advantages of buscopan over atropine or pamine? A. Buscopan does not produce side effects, as, for instance, dilatation of the pupils, blurred vision, dryness of the mouth caused by inhalation of saliva secretion.

Mr. Schimmel: May I ask you to clarify that? You asked him comparing it both with respect to atropine and pamine. Doesn't the answer apply to both?

By Mr. Bailey:

Q. Does your answer apply to both pamine and atropine? A. Yes. It is well known that they both have the same side effects.

38 Q. What about cardiac acceleration? A. Buscopan is far less active in this respect than atropine. It has only one—it is 30 times weaker than atropine, less active.

Q. How does it compare with pamine in cardiac acceleration? A. Pamine is more powerful than atropine is.

Q. Whereas buscopan is only one-thirtieth as active? A. Yes.

Q. What is the objection to these various effects that you have mentioned, namely, the inhalation of saliva, the dilatation of the pupils and the cardiac acceleration? A. I didn't understand you.

Q. What is the objection to them? Why are they undesirable? A. It is very bothersome for the patients. They have less feeling in the dryness of the mouth. They can't swallow or eat. They are unable to go into the bright light because they have the unpleasant feeling of being blinded. They can not read because the eye is unable to focus, and the feeling is very unpleasant.

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41 Mr. Bailey: I offer in evidence as Plaintiff's Exhibit 4, Item W on my list, with a translation of the summary.

Mr. Schimmel: No objection.

The Court: Received.

(Plaintiff's Exhibit 4 was received in evidence.)

42 Mr. Bailey: That being accompanied by a translation.

### Direct Examination (Resumed)

By Mr. Bailey:

Q. Doctor, I hand you Plaintiff's Exhibit 4 and ask you if you are the author of that. A. Yes, I am.

Q. Now in that summary you speak of various results with buscopan, such as the absence of stimulation of the central nervous system, the low pupil dilating effect, and the low toxicity as well as the fact that the pulse acceleration is much less than after atropine, and that the saliva secretion is reduced.

Have you ever tested buscopan on a human being? A. Yes.

Q. On whom did you test it? A. First I think it was myself, and then with other persons in the laboratory.

Q. How much buscopan did you administer to yourself? A. To myself on one day, by injection, 80 to 90 milligrams.

Q. What effects did you notice from it? A. Practically no effects, since I wasn't suffering from spasms or something like that.

43 Q. Would atropine and pamine produce the side effects even in a person who is not suffering from spasms? A. Yes; certainly.

Q. Did you notice any increase in pulse rate? A. No.

Q. Any dryness of the mouth? A. No.

Q. Any interference with your vision? A. No; practically nothing.

Q. You say practically nothing. You did notice a slight— A. Perhaps slight disturbance of focusing for one or two minutes. Then it went away.

Q. And of course the dose was not toxic? A. Not toxic.

Q. You wouldn't be here today if it had been? A. No; it wouldn't be possible.

Q. Have you ever tested buscopan on a human patient who was suffering from spasms? A. No. That has been done in the clinic, the hospital.

Q. Have you tested it in the laboratory on animals? A. Yes.

Q. What effects did it have in so far as relieving
44 spasms in animals was concerned? A. We observed good relief of spasms in the animals. We had to make the spasms artificially by injecting drugs and then we observed, after the injection of buscopan, relief of the spastic conditions.

Q. How did that relief compare with the relief that is given by atropine? A. It was practically the same relief; sometimes a little bit less and sometimes equal to the relief given by atropine.

Q. As a physician, would you expect that a drug which relieved spasms in animals would be similarly effective on human beings? A. Yes; generally.

Q. Did you also observe the effect of buscopan in the increase of pulse rate in animals? A. Yes. We made our comparisons with atropine and we had to increase the dose of buscopan very much to get the same results on the side effects comparable with that of atropine.

Q. I refer you, in Exhibit A, to a chart on page 400 and ask you if those curves represent the increase in pulse rate upon administration to a dog of varying doses of buscopan. A. Yes.

Q. Do those doses, at the rate vary from one-tenth
45 of a milligram per kilogram of body weight to three milligrams per kilogram of body weight? A. Yes.

Q. In a human being, what would that range represent in actual amount of dosage of buscopan? A. That means that the smallest dose, number 1, would be 7.5 milligrams for a normal adult human being, and the highest dose, number 5, would be 3.25 milligrams for a normal human being.

Q. Does Curve 2 on that chart represent approximately a 30 per cent increase in pulse rate? A. Yes, it does.

Q. And that is .5 milligram per kilogram; is that correct? A. One milligram per kilogram.

Q. Curve Number 2? A. Number 2; that is correct; 0.5 milligram.

Q. As far as atropine was concerned, what was your finding as to the relationship between the increase produced by atropine and that produced by buscopan? A. The effect of buscopan in increasing the heart rate is an average of 30 times smaller than atropine.

Q. So that in order to produce that curve number 2—first, as to .5 milligrams per kilogram, what would
46 that be in absolute dosage in a normal human being? A. That would be around 30 to 35 milligrams.

Q. Would it be true that one milligram of atropine would produce about the same pulse rate acceleration? A. Yes.

Q. That is 30 per cent acceleration of the pulse rate? A. Yes.

Q. Whereas it requires 30 milligrams of buscopan? A. Yes.

Q. But expect that effect observed in animals would be equally true upon administration to a human being? A. Yes.

Q. As to the dilating effect on the pupils of the eyes, where you state that the dilating effect of buscopan is 1/500th of atropine, how was that test made? A. In mice. We used several groups of mice. Each group was five mice together. We observed the pupils of the eyes under a microscope. We made a comparison of the effect of the injection of atropine. We measured for every minute, or every fifth minute the diameter of the pupils after the injection of buscopan or of atropine.

Q. Would you expect that difference in dilating effect observed in animals would be equally true in human beings? A. Yes.

47 Q. Would that be true of the reduction in saliva secretion? A. Yes; would be the same.

Q. You observed there in animals that it was fifty times less effective than atropine? A. Yes.

Q. Now I hand you Plaintiff's Exhibits 5 and 6, and I will ask you if pamine bromide is the same as pamine.

(Plaintiff's Exhibits 5 and 6 were marked for identification.)

The Witness: Yes.

The Court: What was that question.

Mr. Bailey: If Pamine bromide is the same as pamine. This article refers to the pamine bromide.

By Mr. Bailey:

Q. Also in Exhibit 6, is methyl scopolamine bromide the same as pamine? A. Yes.

Q. Now, I ask you, Doctor, if you know who Doctor Visscher is, referred to in Exhibit 5? Do you know who Doctor Visscher is? A. I know only he is in the Upjohn Company as a pharmacologist.

48 Q. Is the Upjohn Company the manufacturer of pamine? A. Yes.

Q. What do you find in these two articles as to the effect of pamine as compared with the effect of atropine in mydriasis, by which we mean the dilatation of the pupil, do we not? A. Yes.

Q. I refer you to page 3 of the translation of Exhibit 6, Doctor, near the bottom.

Mr. Schimmel: Talking about 5 or 6?

Mr. Bailey: 6; the translation.

By Mr. Bailey:

Q. What do you find there about the mydriatic effect of pamine? A. I found in two test subjects the mydriatic effect of both substances was practically the same and equally as great and of the same duration as the effect of scopolamine hydrobromide.

Mr. Bailey: Your Honor, I wish to put in, and I would like permission to put in a photostatic copy of this page. It is 557 of Goodman and Gilman, where we have some other pages in evidence.

I have shown this page to Mr. Schimmel and he indicated he would have no objection to my putting in a photostat later on.

49 The Court: All right.

By Mr. Bailey:

Q. Now I call your attention, Doctor, to the table at page 557 of this book and ask you if that shows the comparative mydriatic effect of scopolamine hydro-bromide and of atropine. A. Yes, it does.

Q. The first two items; is that correct? A. Yes.

Q. Which is more active in mydriasis—scopolamine hydrobromide or atropine? A. Scopolamine hydrobromide is a little more effective. May I draw your attention to the fact that this has been tested on local application, one drop in the eye? That is not the exact method we used but it makes no great difference.

The Court: When he says more effective, does he mean more effective in dilation?

The Witness: Yes.

By Mr. Bailey:

Q. Do you have any other knowledge of the comparative effectiveness of scopolamine hydrobromide and atropine when injected in producing dilation? A. By this method, by injection, scopolamine hydrobromide is 2.5 times more active in dilatation of the pupil than atropine.

Q. Is that based on tests that you have made? A. Yes. It is based on our own tests and is in confirmation with other evidence from the literature and the books.

Q. With respect to inhibition of saliva secretion, I call your attention to page 2 of the translation of Exhibit 6, and ask you if you find there any comparison between scopolamine hydrobromide and pamine in inhibiting saliva? A. Yes. There are on page 2, the last two lines, scopolamine hydrobromide and methylscopolamine bromide, Test E and Test O. There is a description of average value for both compounds, 0.06. That means, in other words, they were equally effective on influencing saliva secretion.

Q. How does scopolamine hydrobromide compare with atropine in its inhibition of saliva secretion? A. As far as I know, they are both nearly equal in potency.

Q. Now, with respect to the increase in pulse rate, I refer you to page 4 of Exhibit 6, and ask you—and also to the chart which appears on page 283 of the original—and ask you if you find what amount of pamine was
necessary in order to produce approximately a 40
51 per cent increase in cardiac acceleration. A. May I
have another paper? I find in this table on page 263
that after the administration of a small does of those compounds in question, scopolamine hydrobromide and methyl scopolamine bromide, the dose has been, for each person, .3 milligram. That is a rather small dose.

Q. And what was the increase in heart rate? A. The increase in heart rate after scopolamine hydrobromide was an average of 2 per cent. That is practically no change.

After methyl scopolamine bromide it was increased 39 per cent.

Q. That was on administration of .3 of a milligram; is that correct? A. That is correct.

Q. Would you expect that a slightly smaller does would produce a 30 per cent increase? A. Yes.

Q. And certainly a larger does could not produce a lesser increase? A. No; it would be higher.

Q. Doctor, there is some reference in one of your affidavits in this case to the fact that pamine is 45 times more active than atropine in producing dilation of the
eye.
52 What is that statement based on? A. This state-
ment is based on experiments on local application of solution of atropine and of pamine hydrobromide on the rabbit's eye.

Q. That test gives somewhat different comparative results from what you get by injection? A. Yes.

Q. That is direct application to the eye? A. That is direct local application to the eye.

Q. Have you ever tested any compound of atropine into which a butyl radical has been introduced? A. Yes.

Q. What were the results of those tests? A. This compound is rather toxic and has very weak or feeble spasmolytic activity.

It is not indicated to use it clinically.

Mr. Bailey: I would like to offer in evidence as Plaintiff's Exhibit 7 Item B of the list.

Mr. Schimmel: No objection.

The Court: Received.

(Plaintiff's Exhibit 7 was received in evidence.)

By Mr. Bailey:

Q. Doctor, I hand you Exhibit 7 and ask you if
53 SKF 1637 is one name by which buscopan has been
known. A. Yes.

Q. I refer you to the conclusions there. The first conclusion reads that this material "exerts a profound cholinergic blocking effect upon both gastrointestinal motility and gastric secretion."

Do you agree with that last statement? A. No.

Q. In what do you disagree with it? A. In experiments or clinical observations carried on sometime later, the same author's report, which has not been published, that the effect against gastric secretion is rather poor.

Q. Is it possible to relieve the pain of stomach ulcers without reducing gastric secretion? A. Yes; to some extent; sometimes.

Q. Well, is buscopan effective in relieving stomach ulcers? A. Yes.

Q. That is, the pain of ulcers. A. Yes.

The Court: I am sorry. I missed you there. You read the conclusion here, Mr. Bailey. The doctor does not agree with this conclusion.

54 Mr. Bailey: He doesn't agree with the first conclusion in so far as it states that buscopan inhibits gastric secretion. That was a mistake, apparently, on the part of the authors.

By Mr. Bailey:

Q. Do you agree with the rest of the conclusions there, Doctor? A. Yes.

Q. That the side effects are absent or minimal in the use of buscopan? A. Yes.

Mr. Bailey: I offer as Plaintiff's Exhibit 8 Item F.

Mr. Schimmel: No objection.

The Court: Received.

(Plaintiff's Exhibit 8 was received in evidence.)

By Mr. Bailey:

Q. Doctor, I would just like to read a few parts of the summary of this article. It says:

"... Pendiomid and Buscopan are, as far as their
action on the motility of the small intestine is concerned,
superior and, as far as duration is concerned, equal to
atropine in large doses. Pendiomid in large amounts
may cause collapse. Buscopan has no disturbing
55 side-effects. Banthine essentially corresponds to
atropine, including atropine-like side-effects."

Do you agree with those conclusions? A. Yes.

Mr. Bailey: I would like to offer as Plaintiff's Exhibit 9 Item G.

Mr. Schimmel: No objection.

The Court: Received.

(Plaintiff's Exhibit 9 was received in evidence.)

By Mr. Bailey:

Q. Now, this article, Doctor, states that buscopan induces favorable sedation, especially of the spastic bladder.

The Court: What page are you reading from?

Mr. Bailey: Page 18 of the translation, right at the end.

The Witness: Yes.

By Mr. Bailey:

Q. What is the value of sedation of the spastic bladder? A. That means that it diminishes pain.

Q. What causes the spasms of the bladder? A. The spasms are caused by some irritation of the bladder, by inflammation of spastic conditions.

Mr. Bailey: I would like to offer as Plaintiff's
56 Exhibit 10 Item H.

Mr. Schimmel: No objection.

The Court: Received.

(Plaintiff's Exhibit 10 was received in evidence.)

By Mr. Bailey:

Q. Doctor, in this article it says that ". . . Buscopan represents a drug which is free of side-effects and exerts a remarkable accelerating effect on the process of dilatation and intensifies the activity of labor pains. The preparation is in every respect harmless to mother and baby."

What is the advantage of accelerating or intensifying the effectiveness of the activity of labor pains? A. The time of labor is shortened an average of about 40 per cent, which means the danger time for mother and child is smaller than usual.

Mr. Bailey: I offer as Plaintiff's Exhibit 11 Item IJ.

Mr. Schimmel: No objection.

The Court: Received.

(Plaintiff's Exhibit 11 was received in evidence.)

Mr. Bailey: I might explain the reason I have that
57 IJ is because this folder that I have these in has only one space for the two.

The Court: All right.

By Mr. Bailey:

Q. Now, Doctor, does that article refer to work with buscopan? A. Yes.

Q. Referring to pages 7 and 8 of the translation, the summary states:

"The data . . . on abatement of pain make its advantages clear. Pain disappears more quickly than in controls, and the drug treatment also permits extensive relaxation of diet, bed rest and application of heat."

Is that a correct statement? A. That is correct.

The Court: What page was that?

Mr. Bailey: The summary, beginning at the bottom of page 7.

I offer as Plaintiff's Exhibit 12 Item K on the list.

The Court: Mr. Schimmel?

Mr. Schimmel: No objection.

The Court: Received.

58 (Plaintiff's Exhibit Number 12 was received in evidence.)

By Mr. Bailey:

Q. This item, Doctor, refers to X-ray studies of the effect of new inhibitor pharmacologicals upon the motility of the stomack and the gall bladder.

What is the significance, medically speaking, of the results disclosed in that article? A. In this article is described the effect of motility on the stomach and the gall bladder and it is proved by X-ray studies.

Q. What is the significance of it, medically speaking? Does it show that it relieves some condition? A. It shows that the spastic contractions of the stomach and of the gall bladder are relieved.

Q. Are such spastic contractions at least not an unusual condition in the patient? A. That happens very often.

Q. Does it cause pain? A. And causes pain.

Mr. Bailey: I offer as Plaintiff's Exhibit 13 Item L.

Mr. Schimmel: No objection.

The Court: Received.

59 (Plaintiff's Exhibit 13 was received in evidence.)

By Mr. Bailey:

Q. I ask you if this article refers to the same type of spasms as the preceding article. A. Yes.

Q. I notice in here there is reference to ganglionic blocking. What is meant by that term? A. The nerves' impulses are mediated through nerve cells and in the last ten years some substance of drugs have been known which have a certain effect on blocking these nervous transmissions on the ganglion cell.

Q. That is the ganglion cell.

And the blocking is caused in that path rather than the organ itself? A. That is correct.

Mr. Bailey: I offer as Plaintiff's Exhibit Number 14 Item M.

Mr. Schimmel: No objection.

The Court: Received.

(Plaintiff's Exhibit 14 was received in evidence.)

By Mr. Bailey:

Q. I ask you if that refers to the same type of spasms. A. Yes. 60

Q. Also, I call your attention to page 15 of the translation, to the effectiveness of the drug in three cases of ureterolithiasis and inflammatory diseases of the urinary drainage tract.

What is ureterolithiasis? A. These are stones in the ureter, what is generally called kidney stones, kidney colics.

Q. Relief from those is provided by buscopan; is that correct? A. That is correct.

Mr. Bailey: I offer as Plaintiff's Exhibit Number 15 Item N.

Mr. Schimmel: No objection.

The Court Received.

(Plaintiff's Exhibit 15 was received in evidence.)

By Mr. Bailey:

Q. This document refers to esophageal diagnostics. What is the value of buscopan in that connection? A. The physician is able, by means of buscopan, to see if stoppage of the passage of food in the esophagus is cause by spasms or cancer.

Q. There might be several causes for the stoppage
61 in the esophagus? A. Yes.

Q. One of them might be spasm, and if you administer the buscopan the spasm disappears, and if the stoppage continues you know there is some other cause for it? A. Yes. It is known as functional, and not caused by cancer.

Mr. Bailey: I offer as Plaintiff's Exhibit Number ly Item O.

Mr. Schimmel: No objection.

The Court: Received.

(Plaintiff's Exhibit 16 was received in evidence.)

By Mr. Bailey:

Q. I hand you Exhibit 16, Doctor, which makes reference to the cascade stomach. What is meant by that term? A. The cascade stomach is the kind of stomach which occurs in nervous patients and is due to abnormal spastic conditions of some parts of the stomach, which divide the stomach into two or more different parts.

Q. In other words, the muscles contract so that the stomach is completely closed off, some parts from another? A. Yes.

Q. Is buscopan effective in relief of that condi-
62 tion? A. Yes; as shown by X-ray pictures.

Mr. Bailey: I offer as Plaintiff's Exhibit Number 17 Item. Q.

Mr. Schimmel: No objection.

The Court: Received.

(Plaintiff's Exhibit 17 was received in evidence.)

By Mr. Bailey:

Q. This article, Exhibit 17, refers to the effect of buscopan on the motility of the gall bladder and the summary beginning at the bottom of page 10, states:

"The action of . . . (Buscopan) on the motility of the muscular structures of the gallbladder can be promptly abolished—"

That doesn't seem to read properly,—

"by Buscopan and that the gallbladder reflex is also blocked by the effect of this drug."

A. Yes.

Q. Then it refers to the "clinically tested favorable action on various gall bladder affections by means of buscopan and special effect on dyskinesias."

What is meant by dyskinesias?

What is meant by dyskinesias? A. When the small vessels in the liver which conduct the bile to the gall bladder on a special state of blood functioning and
63 not—

When the small passages between the liver and the gall bladder become contracted by spasms and don't conduct the bile to the gall bladder, buscopan is effective in relieving this spasm and therefore reopening these passages and permit the passage of bile from the liver to the gall bladder.

Mr. Bailey: I offer as Plaintiff's Exhibit 18 Item R.

Mr. Schimmel: No objection.

The Court: Received.

(Plaintiff's Exhibit 18 was received in evidence.)

By Mr. Bailey:

Q. This, again, refers to the use of buscopan and its advantages in shortening labor, does it not? A. Yes.

Mr. Bailey: As Exhibit 19 I offer Item S.

Mr. Schimmel: No objection.

The Court: Received.

(Plaintiff's Exhibit 19 was received in evidence.)

By Mr. Bailey:

Q. Doctor, this refers to the use of buscopan for what purpose? A. For diagnostic purposes.

64 Q. Now, it speaks of salpingo spasms. What is meant by that term? A. This is a duct which leads from the ovary to uterus. If these ducts are under spastic conditions they can be relieved by injection of buscopan or administering buscopan in the form of suppositories.

Mr. Bailey: I offer as Plaintiff's Exhibit 20 Item T.

Mr. Schimmel: No objection.

The Court: Received.

(Plaintiff's Exhibit 20 was received in evidence.)

By Mr. Bailey:

Q. Item 20 refers to improvement of X-ray diagnosis of the urinary tract and it relates to the use of buscopan, does it not? A. Yes.

Q. What is the value of buscopan in that respect? A. It is proved by this article that buscopan is a good help for X-ray examinations of the urinary tract.

Mr. Bailey: May he wait about two minutes for the rest? I have one more of these articles.

The Court: Yes.

Mr. Bailey: As Plaintiff's Exhibit 21 I offer
65 Item U.

The Court: Received.

(Plaintiff's Exhibit 21 was received in evidence.)

By Mr. Bailey:

Q. This refers to the effect of buscopan on renal pressure. A. Yes.

Q. And it states that buscopan—this is page 5, at the bottom of the translation—"is undoubtedly responsible for a marked decrease of pressure in the kidneys and simultaneous prolongation of the interval between individual contractions." A. It indicates that the urine flows more quickly to the bladder than without buscopan.

Q. You mean there is a stoppage? A. Which has been removed. It will dilate it so that the urine can flow quicker and better than before.

(Short recess taken.)

(After recess.)

By Mr. Bailey:

Q. I refer you again to Exhibit 4, Doctor, and at the
top of page 489, there is a table which indicates—
66 what does that table represent? A. That table
represents the mean lethal dose of atropine, scopollamine, and ten other derivatives of scopolamine.

Q. Atropine is the first line? A. Yes.

Q. And buscopan is the third line; is that correct? A. Yes.

Q. On what animals were those tests made? A. These tests have been made on mice, subcutaneous injection.

Q. Is there any comment you wish to make about that table? A. Yes. There is comment about the toxicity of atropine.

Q. What is that comment? A. By mistake we couldn't find out later the true reasons. The toxicity of atropine is not correct here.

Q. What should it be? A. It should be around 750 milligrams per kilogram.

Q. That is in mice? A. In mice; yes.

Q. Does that toxicity apply to human beings? A. No; because in human beings atropine is a highly toxic substance.

Q. What is the toxic dose of atropine? A. The
67 toxic does of atropine on human beings—starting
from 10 milligrams.

Q. 10 milligrams of atropine to a human being may be fatal? A. Yes.

Q. Do you have any knowledge of the lethal dose of pamine? A. Yes; in animals.

Q. But not in man? A. Not in man.

Q. It is true that much greater dosages of buscopan can be given than atropine without fatal effects? A. Yes; without side effects.

Q. I refer you again to Exhibit 3, the Goodman and Gilman book, and particularly on page 560, the section relating to buscopan. A. Yes.

Q. With reference to buscopan having curari properties, what is meant by that expression? A. That expression is meant that after administering of high doses of buscopan, there is a paralysis of the musculature of the arms and legs, and so on.

Q. What dose of buscopan is necessary to produce
68 that effect? A. A dose of about 10 milligrams per
kilogram body weight.

Q. In a human? A. That would be an amount of approximately 750 to 1000 milligrams by injection, rapid intravenous injection.

Q. In the investigation of spasmolytic compounds, what is normally taken as the standard by which their effects are measured? A. As a standard, usually atropine.

Q. It is usually to compare different spasmolytics to atropine? A. Yes.

Q. From that can you then determine the relative effects of two spasmolytics, one with respect to the other? A. Yes.

Q. Is it like specific gravity, where water is taken as the base, and if you know the specific gravity of two compounds you can compare them directly with each other? A. That is exactly right.

Q. By knowing their relative weight as compared with that of water? A. Yes, sir.

Mr. Bailey: Your Honor, I would also like, if Mr.
Schimmel has no objection, to submit as Exhibit 22
69 a fresh copy of Exhibit B, which is attached to my
trial brief here.

Mr. Schimmel: No objection.

The Court: Received.

(Plaintiff's Exhibit 22 was received in evidence.)

By Mr. Bailey:

Q. I show you Exhibit 22, Doctor, and ask you if that table represents, to the best of your knowledge, based on your own tests and on your knowledge of work in the field, the comparative effectiveness of atropine, pamine and buscopan in the inhibition of saliva, cardiac acceleration and pupil extension. A. Yes. I must cite this Value Number 3 here, inhibition of saliva, scopolamine bromobutylate is a little bit less than this figure.

Q. It is less than one-twentieth? A. Yes.

Q. One-fiftieth? A. The correct value would be 0.02.

Q. In each case do you find that the scopolamine bromobutylate in its side effects is very substantially less than atropine, where scopolamine bromo methylate is less? A. Yes.

Mr. Bailey: I don't have a fresh copy unless we
70 take that one right out of the brief.

By Mr. Bailey:

Q. Doctor, is hyoscin another name for scopolamine? A. Yes.

Q. I refer you again to Exhibit 8 in the summary on page 20. There is reference to enteral vegetative dystonia.

Could you tell me in layman's language what that means?

The Court: What is that page?

Mr. Bailey: Page 20.

The Witness: These are patients which are suffering from certain nervous diseases. In other words, if they get into trouble by stress, physically or mentally, they have this kind of reaction, that they get an increased tone and increased movements of their stomach and intestines.

That is what is meant by this expression, "enteral vegetative dystonia".

By Mr. Bailey:

Q. In other words, it would be nervously induced cramps of the intestines, or something like that? A. Yes.

Mr. Bailey: That completes the direct examination.

Cross Examination

By Mr. Schimmel:

71 Q. Doctor, I believe you said that you were familiar with the application involved in this suit, did you not? A. Yes.

Q. And did you not file an affidavit in that application in which you stated that in so far as the spasmolytic power of buscopan is concerned, it was only 1/100th or 2/1000ths as much as atropine? A. Yes.

Mr. Bailey: May I show the witness—

Mr. Schimmel: You can show it to him; certainly. He answered yes.

Mr. Bailey: Go ahead.

By Mr. Schimmel:

Q. In so far as a drug used as a spasmolytic is concerned, would you say buscopan, on the basis of those figures, was better than atropine? A. Yes. There is no contradiction. The explanation is the following: If you try spasmolytics on the isolated gut or intestine, you have to induce spasms artificially. For this purpose you can use acetylcholine, pilocarpine, or, for instance, barium chloride. It depends on the drug you make your experiments with. If they are effective against all the three—spasmogenic compounds are only to one or two—it depends upon the spasmogenic use.

72 Q. Do I understand from that that while it may be 1/1000th as effective as atropine with respect to one agent, it may be entirely different with respect to another agent? A. Yes, it may be. That has not been proved very often; but in this special case we have the evidence that this happens, that buscopan is very weak against spasms when the spasms are induced by acetylcholine, and it is very powerful if the spasms are induced by pilocarpine.

Q. Would it be reasonable to say, in view of what you have just stated, that buscopan does not have general utility as a spasmolytic? A. No.

Q. Would it be reasonable to say, then, that any statement with respect to its spasmolytic power must be related to a specific use or material that had been used to create the spasm? A. No. We can not say that. For instance, clinical conditions would be necessary to know which of the agents produce those spasms.

Q. You are speaking now with respect to the spasm in the animal? A. No; with respect to the spasms in the patient.

Q. I was using animal broadly to cover both human
as well as non-human. You mean in vivo? A. In
73 vivo.

Q. May I ask you this: Are the relative effects of buscopan that you have reported on, were those figures attained with work done on the live animal? A. Yes.

Q. That has been primarily your work? A. Yes.

Q. But the work you have reported on in the affidavit you filed in the case was not; is that a correct understanding of the difference in relative values?

In the affidavit you said that the spasmolytic effect was one-hundredth or two-thousandths as great as that of atropine. A. Yes.

Q. As I understood you, you said those figures with relation not to the live animal; is that correct? A. Also to the live animal, too.

Q. But on an induced spasm? A. When the spasms are induced by injection of pilocarpine or by electrical stimulation of the nerves which causes the organs to contract, then buscopan is quite effective in the order of atropine.

Q. But it may not be as effective if the spasm is induced
by some other material? A. Yes; that is quite
74 correct. It holds also true for atropine, which is
very weak against spasms induced by barium
chloride.

Q. I have here Plaintiff's Exhibit Number 3, which was taken out of the Goodman and Gilman book, certain pages out of the Goodman and Gilman publication.

Nothing was said, I believe, in your direct examination with respect to that publication. What was the publication date of that book, do you remember, from which these pages were taken, Plaintiff's Exhibit 3? A. The date of the publication of this book, Second Edition, 1956.

Q. These pages 542, 552, 559 and 560 were taken out of a book published in 1956. May I refer you to page 560? A. Yes.

Q. In the paragraph under "Scopolamine Butylbromide", may I ask you to read the last sentence in that paragraph? A. (Reading) "The drug is not generally available and considerably more experience will be necessary to determine its clinical value."

Q. As a physician who knows nothing about that specific drug, would that statement give you an answer to the
question of whether scopolamine butylbromide is an
75 effective antispasmodic? A. Yes. It says not too
much about this.

Q. I am referring to the same paragraph. You as a physician knowing nothing about it, would that tell you you could safely use buscopan as an antispasmodic? A. I can not tell how the physician in general practice feels about it.

Q. You are a physician? A. Yes; but not in general practice.

Q. Do you say you are not qualified to say how a general practitioner would consider such a statement from a recognized authority in the field? A. I could not. I have the feeling that the authors of this book are always very careful because this last sentence here is not unusual.

You will find it also when other drugs are described. For instance, atropine, methyl hydrate, or banthine.

Q. In considering— A. May I say popanthylene, on page 564—that is a compound—

The Court: That is beyond what I have.

The Witness: That is beyond. It is a relatively new agent and extensive clinical experience will be required to determine its therapeutic value in relation to the apparent substance and other atropine substitutes.

76 Q. In considering the questions of toxicity of a drug of this specific buscopan, would you say it is more toxic than the base material from which it was obtained? A. It is far less toxic than scopolamine hydrobromide.

Q. I was asking about scopolamine itself. A. That is practically the same.

Mr. Bailey: May we clarify that? I am not quite sure what the doctor means, Mr. Schimmel. Do you mean scopolamine is substantially the same as scopolamine hydrobromide in toxicity? A. Yes.

Mr. Schimmel: The question was with respect to buscopan and scopolamine:

By Mr. Schimmel:

Q. What is the toxicity of buscopan with respect to scopolamine? A. In human beings we have no reports that something has happened with administration of buscopan. We have averaged those of 10 to 20 milligrams by injection and we have used 10 milligrams several times per day only. Up to now we have no reports about some toxicity or remarkable side-effects.

Q. Is buscopan more toxic than scopolamine? A. No; it is less.

77 Q. Is that an unusual thing with respect to the derivatives of the base materials or is it generally true that the derivatives are more toxic than the base material? A. If you compare the base material with the derivatives, simple salt, there is no great effect.

Q. Is butyl atropine more toxic than atropine? A. Yes.

Q. You say butyl scopolamine is not more toxic than scopolamine? A. It is less toxic.

Q. You say it is not more toxic; it is less toxic? A. Yes.

Q. I would like to refer you to page 33 of Plaintiff's Exhibit 1, which is the application in suit. Reading from that page, there is this comparison between atropine, or scopolamine, and scopolamine bromo butylate, in which Item E says the toxicity of the bromo butylate is greater than that of scopolamine.

Do I understand, then, from your experience and what you are saying that that is not a correct statement? A. Yes.

Q. Pamine, I believe—pamine is made according to the Merck patent—scopolamine bromo-methylate—is that correct? A. Yes.

78 Q. You are familiar with that patent, are you not? A. No, sir.

Q. You are not familiar with it? A. No.

Q. How do you know, then, that is the Merck patent, the methylated compound? A. I know that it is made, that it is the same product as described in the Merck patent.

Q. You know that? A. I know that, but I am not familiar with that patent.

Q. Do you know of any ethylated scopolamine being made? A. No.

Q. You never heard of the ethylated compound; is that correct? A. Yes. I have heard about that. But I am not familiar with it.

Q. Can you tell us what you heard about it? A. I know, or what I heard about it, that the ethylated compound is less active concerning spasmolytic activity than the methyl.

Q. And the butylated compound is less active than that? A. When tests are made using acetylcholine as spasmogenoline.

79 Q. Methylated compound is more active than the ethylated compound? A. Yes.

Q. The ethylated compound is more active than the butylated compound? A. Yes.

Q. In other words, they have decreasing activity depending on the increased molecular weight of the alkyl radical that has been added to the scopolamine? A. Yes.

Q. Are you aware of the fact that the plaintiff in this case, who I understand is your employer, filed an application for these butylated scopolamines in Germany? A. Yes.

Q. Can you tell us whether that application became a patent in Germany? A. Yes.

Q. It has been patented in Germany? A. Yes.

Mr. Schimmel: I think that is all I have of this witness, Your Honor.

Mr. Bailey: I just have a few questions.

### Redirect Examination

By Mr. Bailey:

80 Q. Doctor, in spasmolytic activity in the human, how does buscopan compare with pamine? A. As far as I know, the difference is not very great. Maybe that pamine is, on a weight basis, a little bit more effective.

Q. In spasmolytic activity? A. Yes.

Q. Is it possible to give so much larger doses of buscopan that substantially more spasmolytic effect can be obtained with buscopan than with pamine? A. Yes.

Q. Why is that? A. That is because we are able to increase our dose for the reason that no side effects are a limiting factor in raising the doses. You can not do that with atropine or pamine, increase the dose.

Q. Now, Mr. Schimmel read to you from page 33 of the file wrapper a statement in your affidavit that the toxicity of buscopan is greater than that of scopolamine.

I believe you now say it is less than that of scopolamine.

Can you explain how that statement happened to appear?

A. Yes. That means while it has been stated that
81 the toxicity of buscopan is greater than of scopolamine, was based on experiments on animals, it means that the average lethal doses of buscopan are far less than those of scopolamine.

Q. That is true only of animals; is that correct? A. That is only true of animals.

Q. In your affidavit, reference was also made to a statement—this is on page 109 of the file wrapper—that "scopolamine-bromobutylate is only from 1/100 to 2/1000 as powerful as atropine in the tested spasmolytic effect, according to the Nyman tests . . ."

I call your attention to your previous affidavit on page 31, where you speak, in the third paragraph of Nyman investigating certain compounds and you state:

> "According to Straub's method acetylcholine increased the turning of the intestine on the isolated guinea-pig, and the spasmolitic effects of the four substances mentioned were ascertained."

Is that what you meant when you said in your second affidavit "tested according to the Nyman test"? A. That is the same method, using the same spasmogenic agent.

Q. I believe you also testified, did you not, that atropine is ineffective against some spasmogenic materials? A. Yes.

82 For instance, against the spasms induced by barium chloride. Under these conditions, papaverine is the best spasmolytic agent. In this type of action, it is always compared with papaverine and never with atropine, because atropine is practically without effect.

Q. It is true there has been no substantial sale of scopolamine bromobutylate in the United States? A. That is correct.

Mr. Bailey: That is all.

Mr. Schimmel: I have nothing further.

* * * * * * * * * *

Mr. Bailey: * * *

85 I offer as Plaintiff's Exhibit 23 a copy of German patent 145996, issued to the firm E. Merck, together with translation, and I may state, Your Honor, that Mr. Schimmel has agreed that this translation is essentially the same as his, although there may be differences in language, but in essence, the same.

The Court: So you have no objection?

Mr. Schimmel: No objection.

The Court: Received.

(Plaintiff's Exhibit 23 was received in evidence.)

Mr. Bailey: And as Plaintiff's Exhibit Number 24, copy of United States Patent 2305460, to George Scheuing, et al.

Mr. Schimmel: No objection.

I might state those are duplicates of the patents in our folder. We are presenting the same patent.

The Court: Very well. Received.

(Plaintiff's Exhibit 24 was received in evidence.)

86 Mr. Bailey: I ask to be marked for identification as Plaintiff's Exhibit Number 25 a series of six pages of handwritten material.

I only offer them for identification at this time.

(Plaintiff's Exhibit 25 was marked for identification.)

Thereupon,

**William Sager**

was called as a witness by and on behalf of the Plaintiff, and, being first duly sworn, was examined, and testified as follows:

Direct Examination

By Mr. Bailey:

Q. Will you state your name? A. William Sager.

Q. What is your age? A. 39.

Q. Your residence? A. 166 North Columbus Street, Arlington, Virginia.

Q. Occupation? A. Professor of Chemistry.

Q. At what institution? A. George Washington University.

87 Q. What is your educational background? A. I got a Bachelor's degree in Chemistry at George Washington University. I received a Master's degree in Chemistry at the same institution and a Doctor's degree in Chemistry from Harvard University.

I have studied also at Oxford University.

Q. How long have you been at George Washington in a teaching role? A. Eight years.

Q. What other experience have you had? A. I was research chemist at the Texas Company for four years.

Q. Do you do any consulting work? A. Yes, I do.

Q. Would you explain the nature of it? A. Well, I do consulting work with the Bureau of Ordnance, the Navy, and also I consult in problems of chemistry houdry processes.

Q. I hand you copies of Plaintiff's Exhibits 23 and 24 and ask you if you are familiar with those two patents. A. Yes, I am.

Q. Did you at my request carry out certain experiments? A. Yes.

Q. I hand you a copy of Plaintiff's Exhibit 25 for identification, and ask you if you can identify that. A.
These are the notes that I took in connection with
88 the experiments you requested.

Q. You carried out those experiments yourself? A. Yes, I did.

Q. Those notes are in your handwriting? A. Yes, they are.

Mr. Bailey: I offer Plaintiff's Exhibit 25.

Mr. Schimmel: No objection.

The Court: Received.

(Plaintiff's Exhibit 25 was received in evidence.)

By Mr. Bailey:

Q. Now, Doctor, what is the first item there shown on the first page under the date of January 13, 1957? What does that represent? A. Under Run 1, the materials represented, the substances which I mixed on that day in connection with the first preparation.

Q. What was that material that you were trying to produce? A. Scopolamine bromo butylate.

Q. Doctor, I show you Plaintiff's Exhibit 1 and I refer you to page 4 of that exhibit and ask you to compare your

first run with the description in that page. A. The quantities that are employed are in a small fraction of those
on this page, but the proportions are the same.
89 The proportions of scopolamine, of the solvent—

Q. What is the solvent? A. Acetonitrile and butylbromide, the proportions of those three are the same as in Example 1 on this page. The time of the reaction is just about the same, a trifle longer, and the temperature is the same as that in this example.

Q. That is the temperature of 65 degrees c.? A. That is right.

Q. What is the difference in time? A. 164 hours as compared to 160.

Q. Would that in your opinion make any great difference? A. No; not at all.

Q. Will you describe just what you did in carrying out this run? A. The substances were mixed. They were stoppered to prevent escape of the volatile material and permitted to stand at the specified temperature of 65 degrees for 164 hours.

Q. And at the end of 164 hours what did you do? A. The product was—well, the excess solvent was removed. Methyl alcohol was added and the product was then allowed to crystallize.

Q. How long did it take to crystallize? A. I believe I let it stand for a day.

Q. Do your notes show the time? A. It was per-
90 mitted to stand for 5 days.

The product began to crystallize, though, within a few hours. I noticed that.

Q. After it had stood for five days what did you do? A. I chilled the product to complete crystallization, chilled it in an icebox, filtered it and washed it with cold methanol and dried it, dried it in a vacuum oven at 80 degrees.

Q. What was the nature of this material before you dried it? A. It was a nice crystalline transparent substance.

Q. What was the nature after you dried it? A. The crystals had changed appearances. They lost their transparency, which you would expect from the patent.

Q. How do you explain that change in appearance? A. The substance is stated to contain a molecule of methanol of crystallization. On heating at 80 degrees this is driven off and a very porous crystal is left. This changes the appearance. It loses its transparency.

Q. Do you have any of that material, that final material? A. Yes, I do.

Q. Do you have it with you? A. Yes.

Mr. Bailey: I offer the material produced by the witness as Plaintiff's Exhibit 26.

91 Mr. Schimmel: No objection.

The Court: Received.

(Plaintiff's Exhibit 26 was received in evidence.)

By Mr. Bailey:

Q. What was the yield in percentage of the theoretical? A. About 34 per cent.

Q. Did you make any test to find out whether there was other? A. Yes, I did.

Q. What were those tests? A. I added silver nitrate to the filtrate, which is a test for the material which remains in solution.

Q. And what did that indicate? A. That indicated an additional amount which, as I recall, amounted to a total of 59 per cent.

Q. Did you make any tests on this material? A. Yes.

Q. What were those tests? A. I measured optical rotation and melting point.

Q. What was the melting point? A. 142.5 to 144 degrees centigrade.

Q. Where do you find that in your notes? A. On page 4 of the notes.

Mr. Schimmel: What page?

92 The Witness: Page 4, top of the page.

Mr. Schimmel: Mine is page 5.

Mr. Bailey: I must have gotten them in the wrong order.

By Mr. Bailey:

Q. Referring to page 2 of the notes, I note the heading, "Run II". A. Yes.

Q. What does that represent? A. This is a similar preparation of scopolamine bromobutylate, which employs ethyl alcohol as a solvent instead of acetonitrile.

Q. Does Run III use acetonitrile? A. Yes.

Q. Does that correspond to Example II on page 4 of Exhibit 1? A. Yes, it does.

Q. How long was that material allowed to stand? A. 40-some days. It was from February 10 to April 7.

The Court: Are you speaking of Run Number II?

The Witness: Runs Number II and III.

The Court: Both of those?

The Witness: Yes.

By Mr. Bailey:

93 Q. With respect to Run Number III, at the end of that period, what did you do? A. The products were handled as before. The solvent was evaporated, methanol added and the product allowed to crystallize.

Q. Where do you find the description of that in your notes? A. On page 4 and 8. It simply states—and 7 and 8 states that they were collected in the usual fashion.

Q. What did you find as to the material from Run III regarding its properties? A. From all indications it was identical to the material from Run Number I.

Q. Referring to page 5, there is a heading, "Scheuing Procedure." On what was that test based? A. That was based on United States Patent 2305460.

Q. Which example? A. Example Number 1.

Q. And what did you do in carrying out that test? A. The first part of the test involved preparation of scopolamine bromocrotonylate.

Q. How was that done? A. This was carried out by
mixing scopolamine, ethanol and crotyl bromide, which is
also known as crotonyl bromide. The materials were
94 allowed to stand at room temperature for 24 hours
and the product was then collected.

This in turn was dissolved in methyl alcohol and treated with hydrogen in the presence of a catalyst, which was prepared from palladium on activated carbon.

The hydrogen was added until the absorption became very slow.

The catalyst was removed by filtration and the solvent evaporated, and ether added to precipitate the product.

Q. And did you obtain a crystalline product? A. Yes, I did. The crystalline product at first was a poor quality but on re-crystallization from acetonitrile, I was able to get a good crystalline product.

Q. What was the appearance of that product? A. The crystals were small, transparent needles.

Q. Did you heat that product? A. Yes, I did. It was dried in a vacuum oven at 100 degrees.

Q. What happened? A. It became dry but there was no other apparent change in appearance.

Q. Do you have a sample of that material with you? A. Yes, I do.

95 Mr. Bailey: I offer as Plaintiff's Exhibit Number 27 the vial.

Mr. Schimmel: No objection.

The Court: Received.

(Plaintiff's Exhibit Number 27 was received in evidence.)

By Mr. Bailey:

Q. Doctor, would the difference in appearance between Exhibits 26 and 27 be consistent with the materials in those two vials being identical? A. It wouldn't be expected but it wouldn't be absolute proof.

Q. Would the fact that methanol was driven off one and not off the other when you heated them indicate they are different products? A. It would certainly indicate it but, again, it is not absolute proof.

Q. What tests did you make on material of Exhibit 27? A. That was the last one?

Q. The last one. A. I took the melting point of the material and mixed the melting point of the sample of the substance of Run Number I.

Q. What was the melting point of this material?

96 A. The melting point of this material was 193 to 195 degrees centigrade and some darkening was noted on melting.

Q. And what was the melting point when it was mixed with the material of Exhibit 26? A. 116 to 126.

Q. And did you make any other melting point tests? A. Yes, I did. I mixed the material from Exhibit 27 with a known sample of scopolamine hydrobromide.

Q. And what was the melting point obtained? A. The mixture of the pure samples of scopolamine hydrobromide was 195.5 to 197. The mixed melting point with Exhibit 27 and a known sample of scopolamine hydrobromide was 194 to 195.5.

The melting point intermediate between the two substance itself made up the mixture.

Q. Now, Doctor, if the material of Exhibit 26 and that of Exhibit 27 were the same, what would you get in a mixed melting point test? A. If they were the same you would expect that the melting point of the mixture would be the same as the melting point of the highest melting point of the two samples.

Q. In other words, you would expect the melting point in the range of 194 degrees? A. That is right.

97 Q. And you got a melting point in the range of 120 degrees? A. That is right.

Q. Which is lower than either of the melting points of the two materials that you mixed; is that correct? A. That is correct.

Q. Now, as a chemist, what does that indicate to you as to the similarity or dissimilarity of the two materials? A. It means that the materials have to be different.

Q. They could not possibly be the same according to any known chemical theories? A. No, they could not.

Q. What does the melting point test where you mixed scopolamine hydrobromide with the material, Exhibit 27, indicate? A. It indicates that Exhibit 27 is almost certainly scopolamine hydrobromide.

Q. Did you make any other tests other than melting point tests on these materials? A. Yes, I did. I carried out optical rotation measurements on several of the runs.

Q. Did you carry them out with the material of Exhibit 27? A. No, I did not.

98 Did you make any other tests on the material of Exhibit 27? A. No.

Q. Now, with reference to Exhibit 23, did you carry out any tests corresponding to Example 5-B, which appears at the bottom of page 3 of the translation? A. I carried out a reaction which had about the same proportion of substances in it, yes.

Q. Where is that in your notes? A. That is on page 2. The proportion of substances is about the same but there is a substitution of butyl bromide for methyl bromide.

Q. Which run is that? A. Run Number II, on page 2.

The Court: Say that again—substitution of what?

The Witness: Butyl bromide for methyl bromide.

By Mr. Bailey:

Q. How long did you allow that material to stand? A. That stood from February 20 to April 7.

Q. And what results did you get? A. When I removed the solvent and then added ether methanol to precipitate the product, no material was obtained. I also added silver nitrate to determine the amount formed but which remained in solution, and this indicated that the
99 reaction had gone to the extent of about 8 per cent.

Q. That is 8 per cent of the theoretical? A. Yes.

Q. By percentage of the theoretical you mean the percentage of the product that you get, compared to what you would have gotten if all of the materials had reacted completely with each other; is that correct? A. The maximum amount that could possibly be formed.

Q. In other words, when you followed Example 5-B of the Merck patent and applied it to butyl bromide instead of methanol bromide, you got no crystalline product whatsoever after 45 days; is that correct? A. That is correct.

Q. And, on testing, you found that at least in theory, the reaction had proceeded only to the extent of 8 per cent? A. That is correct.

Q. Doctor, do you have any idea how many known organic chemical compounds there are? A. I don't keep up with the exact number, but it is in the order of a million.

Q. And is it true that a person could sit down and write, if he had the time, the formulae in names of millions more? A. Yes.

100 Q. Now, if in 1942 a skilled chemist had been given the name of scopolamine bromobutylate, could he have written the formula for that? A. Yes.

Q. Would he have known its melting point? A. No.

Q. Would he have known its physical properties? A. Only in a rough sort of way.

Q. Assuming that scopolamine bromo methylate was known— A. Yes.

Q. —what would he have expected in so far as the butylate is concerned? A. I think he would have considered that the solubility and various solvents would be in the same general range, that their chemical and physical properties would be parallel, the same in kind but different in degree, perhaps.

Q. Are scopolamine bromo methylate and scopolamine bromo butylate homologous? A. Yes.

Q. What do you mean by homologous? A. Homologous are two members in a family of chemical compounds whose formulas differ by the elements of CH-2, 1 carbon and 2

hydrogens. The adjacent members of this series
101 differ by the elements CH-2.

Q. CH-3 is what? A. Methyl.

Q. And then if you add CH-2, you get C-2-H-5? A. Yes; which is ethyl.

Q. You add another one, C-3-H-7 is what? A. Propyl.

Q. Another one gives you C-4-H-9? A. Yes.

Q. What is that? A. Butyl.

Mr. Bailey: Your Honor, I wonder if I might take that trial brief and take a sheet off the back of it?

The Court: Yes.

By Mr. Bailey:

Q. Doctor, I hand you a sheet and ask you if those formulae are correct as shown thereon. A. There is one error.

Q. Just correct it in pen.

Otherwise they are correct? A. Yes.

Mr. Bailey: I offer the sheet identified by the witness as Plaintiff's Exhibit 28.

Mr. Schimmel: No objection.

102 The Court: Received.

(Plaintiff's Exhibit 28 was received in evidence.)

By Mr. Bailey:

Q. Doctor, is it your opinion that the material produced according to Example 1 of the Scheuing patent is scopolamine hydrobromide? A. It is.

Mr. Bailey: That completes the direct examination.

The Court: Is what?

Mr. Bailey: Scopolamine hydrobromide.

That completes the direct examination.

The Court: Mr. Schimmel.

Cross Examination

By Mr. Schimmel:

Q. Doctor, I am not sure whether I understood you correctly when you were speaking of Exhibit Number 27, which was the product of the Scheuing patent, whether the crystalline product you obtained in that experiment was crystallized from methanol or from the acetonitrile? A. The details are given on my page 5, I think. The reaction itself was carried out in methyl alcohol. Most of this was removed. Some ether was added in accord with the directions of the patent and crystals were obtained at this 103 time, which were re-crystallized from acetonitrile.

Q. What would you say was the solvent which you had when crystallization took place? A. A mixture of methyl alcohol and acetonitrile, with the bulk of the material acetonitrile.

Q. Would you expect crystal formation to be the same in methyl alcohol solvent as acetonitrile solvent? A. You could not predict.

Q. You could not predict? A. No.

Q. Was there anything unexpected, that you got a different physical appearance of the crystals from the example? A. No, not shocking. It could have been either way.

Q. Would you have expected, for example, to have obtained a crystal in the acetonitrile solvent that had, shall we say, crystallized methanol? A. There was a possibility. I wouldn't want to say one way or the other.

Q. If the crystal did not have any crystallization of methanol in it, its appearance would be expected to be different, would it not? A. Yes.

Q. You stated also, I believe, in connection with a question asked by Mr. Bailey, if two materials of different 104 melting points, they are unquestionably chemically different; is that correct? A. No.

Q. Mr. Bailey, I believe, asked you that question. A. I don't believe he did.

Q. If materials differed in melting point, are they different materials necessarily?

Mr. Bailey: Your Honor, I am afraid I must correct Mr. Schimmel. I am certain I did not ask that question of the witness.

By Mr. Schimmel:

Q. Let me ask you, then:

Is it true that materials which differ in melting point are necessarily different as chemical materials? A. No.

Q. Isn't it true that a material may be chemically the same and yet have a different melting point? A. Yes.

Q. So, would you as a chemist say that because the product of Example 1 of Scheuing had a different melting point then the product obtained in your Run I that they would necessarily be different products? A. No.

* * * * * * * * * *

110 Q. I believe you have testified that, given the name scopolamine bromobutylate, there would be no difficulty in the chemist writing the formula for that compound; isn't that correct? A. Yes.

111 Q. I believe you also testified that a skilled chemist could predict in general what the physical and chemical properties of such a compound would be, even without testing it, to determine what those are; isn't that correct? A. Yes; in general, yes. The melting point would be difficult to predict, but solubility, and so forth, you would have a rough idea.

Q. Many of the chemical properties would also be predictable? A. Yes.

Q. And is that true by virtue of the fact that they are due to the fact that the methyl and ethyl compound, scopolamine, are homologous with butyl scopolamine? A. Yes.

Mr. Schimmel: I think that is all I have.

The Court: Mr. Bailey.

Redirect Examination

By Mr. Bailey:

Q. Doctor, in connection with your notes and in particular, page 5, where Mr. Schimmel was asking you about re-crystallizing the product from acetonitrile, why did you do that? Why did you re-crystallize from acetonitrile

in carrying out this experiment? A. First of all, the procedure itself calls for precipitation with ether. The
112 product that was obtained by this method was not
of very high purity. Also, it was difficult to handle in this solvent. The material is too soluble in methanol to precipitate with ether. For that reason I switched it to acetonitrile.

Q. Would you expect that change to have any effect on the chemical constitution of the product? A. Not on the constitution of the product itself. It might change the composition of the crystal if the crystal had a tendency to absorb, or a molecule of methanol of crystallization.

Q. I notice in your notes it says:

"Check crystallization on known scopolamine hydrobromide, same behavior."

Will you explain that? A. When I first ran into this difficulty with the re-crystallization according to the procedure of the patent, I was surprised at the reluctance of the substance to crystallize nicely and so I checked the crystallization procedure on a known sample of scopolamine hydro bromide to see, just to get a better knowledge of how this material might behave, to get some indication if what I had was really scopolamine hydrobromide, and the behavior did seem to be the same. The product was quite soluble with methanol and was difficult to
113 precipitate with ether and they crystallized much
better from acetonitrile.

Q. You told Mr. Schimmel that the fact that two materials are of different melting points doesn't necessarily mean they are different compounds. A. That is correct.

Q. Does it indicate a probability that they are? A. If the melting points are different, it indicates a probability that they are probably different, but there is no certainty.

Q. But your mixed melting point test in your opinion proved beyond a doubt that they are different; is that correct? A. That is correct.

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121 The Court: Have you anything you would like to put in, Mr. Schimmel?

Mr. Schimmel: Other than what I handed to Your Honor, our official exhibit.

I might formally introduce it into evidence—Defendant's Exhibit 5A to D, constituting a copy of the patent of Scheuing, et al., 2305460; a copy of the Merck German patent 145996, and a translation thereof; a copy of the Examiner's statement before the Board of Appeals in the Patent Office, and a copy of the decision of the Board of Appeals.

122 The Court: No objection?

Mr. Bailey: No objection.

The Court: Received.

(Defendant's Exhibit Number 1 was received in evidence.)

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177 Filed April 18, 1957

**Opinion of the Court**

April 17, 1957

Jennings Bailey, Jr., Esq.
1317 F Street, N. W.
Washington 4, D. C.

Attention: Mc. Schimmel.

E. L. Reynolds, Esq.,
Solicitor,
United States Patent Office,
Washington 25, D. C.

In re: Civil Action No. 3069-55,
*C. H. Boehringer Sohn* v. *Watson.*

Gentlemen:

Upon further consideration of the evidence and argument in the above case, I have concluded that neither the product nor process claims are patentable over the prior art.

As to the process claims, plaintiff's witness, Doctor Sager, testified that the applicant's variations of time and heat, which distinguished its process from that disclosed in the Scheuing patent, were procedures which would have been indicated to any skilled chemist.

As to the product claim, conceding great utility in Buscopan because of an unexpected degree of freedom from undesirable side effects, and assuming (without deciding) that there was no anticipation by the mere naming of scopolamine bromobutylate in the Scheuing patent accompanied by a further description which showed the error of such naming, and assuming further (without deciding) that the applicant is not estopped to impeach its own prior patent, I find that applicant's product does not come within the rule permitting patent of homologues possessing new and unexpected properties, inasmuch as the Merck patent disclosed that bromides of derivatives of the scopoleine group are advantageous as compared with the original alkaloids, in that they are either entirely lacking in undesirable secondary effects, or at least these are greatly diminished, whereas the desired properties of the plant bases are retained in them.

Counsel for the defendant will please prepare and submit promptly appropriate findings of fact, conclusions of law, and order.

Very truly yours,

(Signed) R. B. KEECH

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178 Filed May 6, 1957

## Findings of Fact

1. This is a civil action brought under the provisions of Section 145 of Title 35 United States Code wherein plaintiff, as assignee of the patent application of Franz Adickes, Serial No. 251,840, filed October 17, 1951, entitled "Scopol-

amine-Bromobutylate and Process of Producing Same", seeks a judgment from the court authorizing the defendant, Commissioner of Patents, to grant a patent to plaintiff based upon certain claims of said application.

2. The claims before the court are those numbered 5 to 10 incl., 12 and 13 in the aforementioned application, as appears from paragraph V of the complaint.

3. Claims 5 to 9 incl., 12 and 13 at bar, of which claims 5 and 12 are illustrative, define a process of producing quaternary scopolamine-bromobutylate by mixing a scopolamine base with an excess of butyl bromide, the mixture being dissolved in an organic solvent and allowed to stand for at least one month (claim 12) or heated to an elevated temperature up to about 65° C (claim 5) to permit or
179 cause reaction to take place, and then dissolving the reaction product in an organic solvent, from which the reaction product crystallizes out, residual solvent being removed from the crystallized product by drying.

4. Claim 10 defines as a new product quaternary scopolamine-bromobutylate having a melting point of about 140° to 144° C and having a specified structural formula.

5. The specification of the application at bar describes the alleged invention as one concerned with the production of the product defined in claim 10 by the reaction of the scopolamine base with an excess of butyl bromide dissolved in an organic solvent of strong polar character, such as acetonitrile, chloroform, alcohol and acetone. Two specific examples are set forth. In one, the reacting materials dissolved in acetonitrile are heated under reflux to 65° C for between six and seven days, after which the oily reaction product formed is dissolved in hot methyl alcohol and crystallization allowed to take place. In the other, the same reactants and solvent are allowed to stand for six months at room temperature, with crystal formation beginning after 1 to 2 months. The scopolamine-bromobutylate so produced is said to have importance as a spasmolytic, being

at least as effective as atropine for this purpose, and having decreased toxicity and decreased undesirable side effects.

6. The prior art relied upon by defendant as negativing invention and patentability is:

180 German patent to Merck, No. 145,996, granted November 2, 1903, which describes methods for the preparation of bromo-alkylates of alkaloids, including but not limited to the bromo-methylates and bromo-ethylates of scopolamine, by the action of the alkyl bromide at ordinary temperature on the alkaloid base or their solutions in alcohol, acetone, chloroform or similar solvents. The specific examples describe the production of scopolamine bromo-methylate from scopolamine and an excess of methyl bromides, with or without a solvent, by allowing the mixture to stand for 2 days at room temperature. The initial reaction product is recrystalized from alcohol-ether solution. Merck specifically discloses only the bromo-methylate and bromo-ethylate.

7. Plaintiff's process is distinguished from that disclosed in the Merck patent by variations of time and heat, according to the testimony of plaintiff's witness. These procedures would have been indicated to any skilled chemist.

8. The differences between the process sought to be patented and the prior art process are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

9. Claims 5 to 9, inclusive, 12 and 13 define no invention in view of Merck German Patent No. 145,996.

181 10. Claims 5 to 9, inclusive, 12, and 13 are unpatentable, in view of Merck German Patent No. 145,996.

11. The product defined in claim 10 at bar, scopolamine bromo-butylate, has great utility because of an unexpected degree of freedom from undesirable side effects.

12. The product defined in claim 10 at bar is a homologue of the bromethylate and bromethylate derivatives of scopolamine disclosed in the Merck patent.

13. The Merck patent states that bromides of alkyl derivatives of scopolamine are advantageous as compared with the original base alkaloid, in that they are either entirely lacking in undesirable secondary effects or at least these are greatly diminished, while retaining the desired properties of the alkaloid base.

14. The product defined in claim 10 at bar does not possess new and unexpected properties, sufficient to impart patentability.

15. Claim 10 is unpatentable in view of Merck German Patent No. 145,996.

### Conclusions of Law

1. Plaintiff is not entitled to a patent containing any
of claims 5 to 10, inclusive, 12, and 13 of the
182 patent application of Franz Adickes, Serial No.
251,840, filed October 17, 1951, involved in this proceeding.

2. Plaintiff is not entitled to a patent containing any of the claims enumerated in paragraph V of the complaint.

3. The complaint should be dismissed as to all the claims.

R. B. Keech
*Judge*

May 6th, 1957

184 Filed May 6, 1957

### Judgment

This action came on to be heard at this term, and thereupon upon consideration thereof, it is this 6th day of ............, 1957

ADJUDGED that the complaint be and it is hereby dismissed, with costs against the plaintiff.

R. B. KEECH
*Judge*

APPROVED AS TO FORM:
JENNINGS BAILEY, J
*Attorney for Plaintiff*

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185 Filed May 15, 1957

### Motion for Modification of Judgment and for New Findings of Fact

This motion is brought under Rule 59 FRCP, seeking amendment of the judgment herein, together with additional findings of fact.

The motion is restricted to the product claim, claim 10. As to this claim, plaintiff urges that the ruling of the Court is clearly erroneous and should be modified, for the reasons set forth in the accompanying memorandum.

Plaintiff moves:

I. That the Court make the following additional findings of fact:

16. As a matter of fact, the ethyl and methyl scopolamine bromides have substantially greater side effects than scopolamine in cardiac acceleration, inhibition of saliva and dilatation of the eyes, whereas scopolamine bromobutylate is substantially free of any such side effects.

II. That the Court amend findings 14 and 15 to read as follows:

14. The product defined in claim 10 is sufficiently different in its properties from the compounds disclosed in the Merck patent to impart patentability thereto.

15. Claim 10 is patentable.

186 III. That the Court amend the conclusions of law to read as follows:

1. Plaintiff is not entitled to a patent containing any of claims 5 to 9, inclusive, 12 and 13 of the patent application of Franz Adickes, Serial No. 251,840, filed October 17, 1951, involved in this proceeding.

2. Plaintiff is entitled to a patent containing claim 10.

3. The complaint should be granted as to claim 10 and dismissed as to the remaining claims.

IV. That the Court order the amendment of the judgment to read as follows:

"This action came on to be heard at this term, and thereupon upon consideration thereof, it is this day of , 1957

"ADJUDGED that the complaint be granted as to claim 10 and dismissed as to the remaining claims, with costs against the plaintiff."

Respectfully submitted,

JENNINGS BAILEY, JR.
Jennings Bailey, Jr.
1317 F Street, N.W.
Washington 4, D. C.
*Attorney for Plaintiff*

Considered and denied.

R. B. KEECH, J.
6/10/57

187 Filed Aug. 6, 1957

## Notice of Appeal

Notice is hereby given that C. H. Boehringer Sohn, defendant above named, hereby appeals to the United States Court of Appeals for the District of Columbia Circuit from the final judgment entered in this action on the sixth day of May, 1957, and the order denying the Motion for Modification of Judgment and for New Findings of Fact entered on the tenth day of June, 1957.

JENNINGS BAILEY, JR.
Jennings Bailey, Jr.
*Attorney for Plaintiff-Appellant*
1317 F Street, N.W.
Washington 4, D.C.

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194 CIVIL DOCKET

## UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

### Proceedings

Date

1955

July 13—Complaint, appearance filed.

July 13—Summons, copies (1) and copies (1) of Complaint issued. Atty Gen ser 7-18-55 ser 7-14-55; U.S. Atty ser 7-14-55.

July 22—Answer of deft to complt; c/m 721-55; app of E. L. Reynolds for deft; filed.

July 22—Calendared (N).

1957

April 10—Trial brief of pltf; c/m 4-10-57. filed.

April 12—Hearing begun & respited to 4-15-57. (Rep. B.O. Watson) Keech, J.

April 15—Hearing resumed & respited to 4-16-57. (Rep. B.O. Watson) Keech, J.

April 16—Hearing resumed; argued & submitted. (Rep. B.O. Watson) Keech, J.

April 18—Letter from Judge Keech to Jennings Bailey and E.L. Reynolds dated 4-17-57. filed.

May 6—Findings of Fact & Conclusions of Law. filed.

May 6—Judgment dismissing complt & awarding deft. cost. (N) Keech, J.

May 15—Motion of pltf. for modification of judgment & for new findings of fact; c/mailing memorandum. filed.

June 11—Motion for modification of judgment & for new findings of fact. Considered & denied 6-10-57. (fiat) micro 6-11-57. Keech, J.

June 11—Opposition of deft's motion for modification of judgment etc. (Received Judge Keech 6-10-57) filed.

June 17—Reply memorandum of pltf. in support of motion to modify, etc; c/m 6-17-57. filed.

Aug. 6—Notice of appeal by pltf. from orders of 5-6-57 & 6-10-57, Copy to Mr. Schimmel, deposit $5.00 by Bailey.

Aug. 6—Cost bond on appeal of pltf. with Fidelity and Deposit Co. of Md. in sum of $250.00 approved & filed.

Aug. 6—Designation by pltf. of record on appeal. filed.

Aug. 6—Statement by pltf. of points on appeal. filed.

Aug. 7—Order extending time for filing record & docketing appeal to Oct. 15, 1957. (N) Tamm, J.

Sep. 25—Transcripts of proceedings 4-12-57, 4-15-57, & 4-16-57. B.O. Watson, reporter. filed.

Sep. 26—Exhibits of pltf. 1-28. filed.

# EXHIBITS

## Excerpts From Plaintiff's Exhibit No. 1

## Specification

Franz Adickes, Georg-Scheuing-Strasse 15,
Ingelheim, Germany.

## "QUATERNARY SCOPOLAMINE-BROMOBUTYLATE AND PROCESS OF PRODUCING SAME."

The present invention is concerned with the production of scopolamine-bromobutylate which possesses remarkable therapeutic properties.

According to the invention the production of scopolamine-bromobutylate takes place by action of excess n-butyl bromide on scopolamine-base, dissolved in organic solvents. It is preferable to employ an organic solvent of a strong polar character, as for example acetonitrile. Other organic solvents which come into question for the carrying out of the process according to the invention are, for example, chloroform, alcohol and acetone. If butyl bromide is used in excess, one may, if desired, work without a solvent.

The scopolamine-bromobutylate obtained according to the invention crystallises out relatively slowly, and if one works at elevated temperatures, for example at 65° C, a reaction time of a week and more comes into question. On working at room temperature the reaction time can amount to half a year and more. By inoculating the reaction mixture with crystals of scopolamine-bromobutylate the time up to inception of crystallisation can be shortened.

In German patent specification No. 698,274 a process for the production of quaternary scopolamine salts is described, which is said to apply also to scopolamine-bromobutylate. As has been proved the information contained in the said German patent specification is based on an error and no quaternary scopolamine salts, in particular no scopolamine-bromobutylate is obtained according to the process there described. The statement that no quaternary scopolamine salt can be obtained from scopolamine base and the corresponding alkyl esters of strong acids in the usual way, is also based on an error.

In German patent specification No. 698,274 a melting point of 195-197° C is given for the scopolamine-bromobutylate. Actually however this compound has been shown to have a melting point of 142-144° C as obtained by the process according to the invention and made pure.

Also the information contained in the German patent, to the effect that scopolamine-bromobutylate is some ten times more strongly active than scopolamine in rabbits eyes is not correct. Actually the activity of scopolamine-bromobutylate is at least 200 times less effective than that of scopolamine and about 500 times less effective than that of atropine. By reason of this advantageous property as well as the fact that with scopolamine-bromobutylate the action on the heart amounts to only 1/30th that of atropine, whilst the action on the stomach, gut and gall bladder is about equal to that of atropine and the far-reaching non-toxicity, scopolamine-bromobutylate has a very extraordinary importance as a spasmolytic.

In the following the carrying out of the invention will be further explained by means of two working examples.

### Example 1.

1300 g. Scopolamine base are heated under reflux in an oil bath to 65° C for 160 hours with 600 ccs. purified acetonitrile and 350 g. n-butylbromide with frequent shaking. The resulting oily layer is allowed to settle and the upper liquid is driven off. The oily layer is dissolved in the hot in methyl alcohol and crystallisation allowed to take place. The scopolamine-bromobutylate crystals are filtered off with suction and if desired, recrystallised once more from methyl alcohol. As they contain still one molecule of methyl alcohol of crystallisation, they are dried in vacuo at 80° C to constant weight M.P. = 142-144° C, $[\mathrm{oc}]_{D}^{20} =$

—20.5,—20.8° (3% aqueous solution, 2 dm tube). The yield of pure substance amounts to about 65% of theory.

EXAMPLE 2.

1300 g. Scopolamine base are dissolved in the hot in 900 ccs. acetonitrile and mixed with 2500 g. n-butylbromide. This is allowed to stand for six months at room temperature with frequent shaking. After 1 to 2 months crystal formation commences which may be accelerated by inoculating the reaction mixture with scopolamine-bromo-butylate crystals. After complete reaction of the starting components the crystals formed are recrystallised from methyl alcohol. The yield of pure material amounts to over 70% of theory.

By fractional crystallisation still more scopolamine-bromobutylate may be obtained from the mother liquor.

As elevated temperatures should in general be avoided in the preparation of quaternary salts it is recommended to work with as a low a temperature as possible in the process according to the invention. The yields obtained by working at 20° C according to Example 2 are for this reason better than those obtained by working at 65° according to Example 1.

WHAT I CLAIM IS:

1. Process for the production of scopolamine-bromobutylate characterised in that excess n-butyl bromide is allowed to act on scopolamine base dissolved in organic solvents.

2. Process according to claim 1 characterised in that the reaction is carried out in solvents of strong polar character, as for example acetonitrile.

3. Process according to claim 1 or 2 characterised by a several day inter-action of the starting material at elevated

temperature or by a several months action at ordinary temperature.

4. As a new product the scopolamine-bromobutylate.

### Oath. Power of Attorney and Petition

I, FRANZ ADICKES, having been duly sworn, depose and say, that I am citizen of Germany residing at Georg-Scheuing-Strasse 15, Ingelheim, Germany; that I have read the foregoing specification and claims and I verily believe that I, FRANZ ADICKES am the original, first and joint inventor of the invention or discovery in "PROCESS FOR THE PRODUCTION OF SCOPOLAMINE-BROMOBUTYLATE" described and claimed therein; that I do not know and do not believe that this invention was ever known or used before my invention or discovery thereof, or patented or described in any printed publication in any country before my invention or discovery thereof, or more than one year prior to this application, or in public use or on sale in the United States for more than one year prior to this application; that this invention or discovery has not been patented in any country foreign to the United States on an application filed by me or my legal representatives or assigns more than twelve months before this application; and that no application for patent on this invention or discovery has been filed by me or my representatives or assigns in any country foreign to the United States, except as follows:

German Patent Application B 13 196 IVc/12p, filed Dec. 27th, 1950.

I further declare that this invention was made after January 1st, 1946.

And I hereby appoint HARRY C. BIERMAN, of 545 Fifth Avenue, New York, N.Y., Registration No. 11.077, my attorney with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith.

Therefore I pray that Letters Patent be granted to me for the invention or discovery described and claimed in the foregoing specification and claims, and I hereby subscribe my name to the foregoing specification and claims, oath, power of attorney, and this petition this 8th day of October, 1951.

FRANZ ADICKES
Franz Adickes
Georg-Scheuing-Strasse 15, Ingelheim, Germany

(Post-Office Address)

**Acknowledgement**

} ss.:

Before me personally appeared FRANZ ADICKES, to me known to be the person described in the above application for patent, who signed the foregoing instrument in my presence, and made oath before me to the allegations set forth therein as being under oath, on the day and year aforesaid.

PIERSON M. HALL
(Seal) *V-Consul*

Paper No. 3

## DEPARTMENT OF COMMERCE

United States Patent Office ..

Washington

Applicant: Franz Adickes
Ser. No. 251,840
Filed Oct. 17, 1951
For Process for the Production of Scopolamine-Bromo-butylate

Harry C. Bierman
545 Fifth Ave.
New York, N. Y.

This application has been examined.

References made of record:

| | | | |
|---|---|---|---|
| Scheuing et al | 2,305,460 | Dec. 15, 1942 | 260-292 |
| Merck (German)<br>(2 pgs spec.) | 145,996 | Nov. 2, 1903 | 260-292 |

The oath is objected to since "joint" is used instead of "sole". A new oath is required.

Claims 1, 2, and 3 are rejected as unpatentable over Merck in view of Scheuing. Merck teaches the reaction of scopolamine with methyl bromide in alcohol to form scopolamine-bromo-methylate. To use this method to form the higher homolog, butylate, of Scheuing is not deemed invention.

Claim 2 is further rejected as failing to particularly point out the alleged invention in the recitation of "as for example acetonitrile".

Claim 3 is further rejected as alternative since it depends on any one of two claims and recites "temperature or by".

Claim 4 is rejected as fully met by Scheuing et al who teaches scopolamine-bromobutylate. Even if as alleged by applicant, if the compound produced is not actually scopolamine-bromobutylate, the conception of the compound is still taught by Scheuing et al. so that claim 4 is unpatentable over this disclosure.

Claims 1-4, inclusive, are rejected.

Examiner

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IN THE UNITED STATES PATENT OFFICE

Div. 6
In re Application of Franz Adickes
Serial No. 251,840
Filed October 17, 1951, for
Process for the Production of Scopolamine-Bromobutylate

October 1, 1952

Hon. Commissioner of Patents
Washington, D. C.

Sir:

Responsive to the Examiner's letter of April 11, 1952, please amend the application as follows:

Cancel the claims and insert the following—

5. A process for producing scopolamine-bromobutylate which comprises mixing scopolamine base with an excess of butyl bromide, dissolving said mixture in a solvent of strongly polar character, heating said solution to a temperature of about 65° C. but insufficiently high to cause decomposition to take place, dissolving the reaction product in an organic solvent, allowing said product to crystallize, and drying the product to remove residual solvent.

6. A process according to claim 5 in which the reaction mixture is inoculated with crystals of scopolamine-bromobutylate.

7. A process according to claim 5 in which the polar solvent is acetonitrile.

8. A process according to claim 5 in which the organic solvent is methyl alcohol.

9. A process according to claim 5 in which the temperature is maintained for several days.

10. As a new product scopolamine-bromobutylate having a melting point of about 142° to 144° C.

11. As a new product scopolamine-bromobutylate having a melting point of about 142° to 144° C., and produced by heating a mixture of scopolamine and butyl bromide dissolved in a strongly polar solvent to a temperature of about 65° C. for several days and recrystallizing from an organic solvent.

## REMARKS

The Examiner has noted an objection to the oath and requires that a new oath be filed. It is requested that the requirement be held in abeyance until patentability of the claims has been demonstrated.

In view of the objections which the Examiner has noted to the claims, a new set of claims is submitted herewith which is believed to clearly distinguish from the prior art cited by the Examiner. The patent to Scheuing describes the manufacture of a compound which is called scopolamine brom-butylate. However, as will be demonstrated, this compound is actually not formed according to the patentee's process. He first reacts scopolamine with crotonyl bromide and treats the product with hydrogen in the presence of a catalyst. He assumes that hydrogenation takes place but actually there is a splitting off of the crotonyl group and the formation of the brom-hydrate. This is well-known in the literature, as for example, the article by H. Emde appearing in Arch. Pharm. 244 (1906); 289 Helv. chem. act. 15 (1932) 1330. He has there demonstrated that when compounds having an N-C linkage are treated with hydrogen, the double bond is not hydrogenated but the organic radical is split off. There are many instances in the prior art of this and reference may be made to the article by Huisgen, Wieland u. Eder—Liebigs Ann. Chem. 561/193 (1949), which is to the same effect. Therefore, following the patentee's process, applicant's product is not formed. This is further demonstrated by the fact that the patentee's purified product has a melting point of 195° to 197° C. Quite to the contrary, applicant's product has a melting point of 142° to 144° C. There can be no question but that applicant's process produces an entirely different final product.

The Examiner has also cited a German patent to Merck, stating that it teaches the reaction of scopolamine with methyl bromide. The patentee formed the brom-methylates of alkaloids of the atropine and scopolamine groups. Only in Example 5 is there a description of the methylated scopolamine compound. The reaction is at room temperature for about two days when the crystalline product is precipitated. It is significant that the reaction goes along readily in a relatively short time and that quantitative results are obtained. The Examiner realizes that the description is not of applicant's compound but of the brom-methyl derivative and scopolamine. It appears to be the Examiner's opinion that the substitution of the butyl bromide for the methyl bromide in the reaction would not constitute invention. However, if one does this, practically no results are obtained. After two days there is no precipitation whatsoever of any product. Even after fourteen days standing at room temperature, no crystallization has taken place. Therefore one would assume that while the reaction goes on very readily with the methyl compound, it becomes more difficult and with the butyl compound, it does not take place at all. Therefore, applicant's modification of the process which gives a commercial yield of the brom-butylate, is most unexpected. Applicant has succeeded in causing the reaction to take place in a relatively short time, namely, a few days, at elevated temperatures. A temperature of up to 65° to 70° C. gives a large yield in a very few days. One should not maintain a temperature substantially higher as decomposition of reactants and products takes place. Applicant in his process utilizes a strongly polar solvent and this together with the elevated temperature is important in giving commercial results. No such steps are set forth in the Merck patent and the results are unexpected. Therefore, this patent cannot anticipate the process claims.

The Examiner has suggested a combination of the two patents but there is no logical way in which a butyl bromide could be substituted in the process of Scheuing. He has a two stage operation, in the first of which it is necessary for an unsaturated bromide to be used. To use a saturated bromide in the first step would destroy the patentee's invention, which is in the formation of unsaturated alkyl compounds.

The Examiner in rejecting claim 4 has stated that Scheuing describes the scopolamine bromobutylate. While the patentee uses this term, he actually does not obtain the compound as set forth above. He obtains the hydrate since the literature shows that the crotonyl is not hydrogenated but is split off so that the butyl radical is never formed.

The patent in column 1, lines 20 to 22, does refer to a butyl compound of scopolamine, stating that it is ten times as strong in dilation of the eye as scopolamine. This compound is different from applicant's, as will be demonstrated below since applicant's product is far weaker in its action on the eye than scopolamine.

Applicant's product has properties that are so totally different from the brom-methyl derivative that there is no comparison between them. While chemically they may be in an analogous series, from the pharmacological standpoint they are entirely different. The prior compound has so many unfavorable properties that it cannot be used for the same purpose as applicant's product. This is adequately shown by the literature and by the experiments of applicant's assignee.

Considerable work was done by E. Nyman in determining the pharmacological properties of atropine and other compounds including scopolamine bromohydrate and methyl scopolamine. His work is reported in Acta Physiol. Scand. *6,* 256, 1943; Acta med. scand. *118,* 466, 1944. Among many other factors determined by the author, he found that the toxicity to animals of the quaternary nitrogen compounds is three times as high as the toxicity of the starting materials. Such higher toxicities would elimnate the use of the quaternary nitrogen compounds since atropine and scopolamine are available.

The author also found that the effect of the bromohydrate and the methyl derivative in stopping saliva secretions had been multiplied. For instance, atropine has a value of 1, on which basis the bromohydrate has three times the effect and the methyl derivative has 3.6 times the effect. As is readily realized, this is a most undesirable side reaction.

Similarly the author determined the relative dilation of the pupil of the eye in human beings. Considering atropine to have an activity of 1, the bromhydrate and the methyl derivative were three times as effective in dilation. This is also an undesirable property and decreases the value of these derivatives.

Experiments were conducted by Roost et al, reported in Schweiz. Med. Wschr. 1947, 1284, on the methyl derivative. They found that the antagonism thereof against acetylcholine was four times as great as atropine, which is a most undesirable result.

Applicant's assignee has also conducted experiments on the methyl derivative with relation to the frequency of the heart beat. It was found that the acceleration of the methyl derivative was about four times as great as the acceleration caused by the starting material, namely, scopolamine. Such a result could not be tolerated in medical practice.

In addition to the above mentioned undesirable side reactions, it was also found that there was undesirable dryness in the throat and a disturbance in vision.

It has also been found that paralysis of the peripheral nerve endings of the vagus takes place with the prior used atropine, scopolamine and the quaternary methyl compound. Since such is the case it would be assumed that the butyl derivative would likewise paralyze the action of the intestines. However, it is quite surprising that applicant's product does not cause any paralysis of the ganglia.

As a result, we may list the various properties which totally distinguish applicant's product from the prior substances used for applicant's purpose. They are as follows:

1. The acceleration of the heart beat by applicant's product in the case of dogs which have not been narcotized is less than one-thirtieth of the acceleration which results from atropine or scopolamine.

2. The dilation of the pupil in white mice in the use of applicant's product is more than five hundred times weaker than the dilation caused by atropine or scopolamine.

3. The stoppage of the saliva secretion of cats which have been narcotized is about fifty times weaker than the stoppage caused by atropine or scopolamine.

4. The lowering of the tone of the isolated intestine after treatment with acetylcholine when using applicant's product is from 100 to 500 times weaker than the effect obtained by atropine or scopolamine.

5. The toxicity of applicant's products relative to that of atropine is less than one-third thereof.

The above properties are most desirable in applicant's duct and they could not be expected to be obtained from a knowledge of the prior compounds such as those described in the two patents of record. As further demonstrating the unexpectedness of the introduction of the butyl group, it has been found that when one forms a quaternary compound of atropine with the introduction of the butyl radical, the resulting compound has been so weakened in its pharmacological properties that it is now unsuitable for therapeutic application. This was established by Wick, reported in Arch. f. Exp. Path. u. Pharmakol. *213,* 485, 1951. In view of this the Examiner must realize that the prior knowledge would have led an investigator away from attempting to introduce the butyl radical into compounds of the scopolamine type. Therefore, the claims cover a most unexpected discovery, and allowance thereof is requested.

Respectfully submitted,

*Attorney for Applicant.*

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Paper No. 7

DEPARTMENT OF COMMERCE

UNITED STATES PATENT OFFICE
WASHINGTON

Applicant: Franz Adickes
Ser. No. 251,840
Filed Oct. 17, 1951
For Process for the Production of Scopolamine-Bromobutylate

Harry C. Bierman
545 Fifth Ave.
New York, N. Y.

Responsive to amendments filed October 2, 1952, October 10, 1952 and November 17, 1952.

Claims 5-13, inclusive, remain in the case.

Claims 5-9, inclusive, 12, and 13 are rejected as unpatentable over Merch in view of Scheuing et al. Merck teaches the reaction of scopolamine with methyl bromide in alcohol to form scopolamine-bromomethylate and dissolving the reaction mixture in alcohol to permit the product to crystallize. No invention is seen in using the method of Merck to produce the higher homologue, scopolamine-bromobutylate of Scheuing et al.

Claims 10 and 11 are rejected as unpatentable over Merck who teaches the lower homologue, scopolamine-bromoethylate.

Claims 10 and 11 are further rejected as unpatentable over Scheuing et al. who disclose scopolamine-bromobutylate (page 1, column 1, lines 17-22, and column 2, lines 26 and 27). Even, if, as alleged by applicant, the compound produced by the method of Scheuing et al, is not actually scopolamine-bromobutylate, the conception of the compound is still taught by Scheuing et al. so that the product claims are unpatentable over this disclosure. (Merck & Co. v. Marzall, 93 U. S. P. Q. 355; In re Von Bramer et al., 127 F2d 149).

Claim 11 is further rejected as an improper product claim since, although the structure of the product is known, the product is recited by its process of manufacture. (Ex parte Fesemmeier, 1922 C. D. 18).

Since an issue appears to have been reached, the rejection of claims 5-13, inclusive, is made FINAL.

Examiner

Paper No. 9

DEPARTMENT OF COMMERCE

UNITED STATES PATENT OFFICE
WASHINGTON

Applicant: Franz Adickes
Ser. No. 251,840
Filed Oct. 17, 1951

Harry C. Bierman
545 Fifth Ave.
New York, N. Y.

Responsive to amendment and affidavits filed June 24, 1953, after final rejection.

The amendment has not been entered since it does not place the case in condition for allowance. The amendment will be entered for purpose of appeal. The affidavits have been carefully considered but are not considered sufficient to overcome the rejection of the process claims or the product claim on Scheuing et al. for the reasons of record.

This case will be abandoned unless placed in condition for allowance or appeal is taken on or before November 18 1953.

Examiner

IN THE UNITED STATES PATENT OFFICE

Div. 6
In re Application of Franz Adickes
Serial No. 251,840
Filed October 17, 1951, for
Process for the Production of Scopolamine-Bromobutylate
June 23rd, 1953

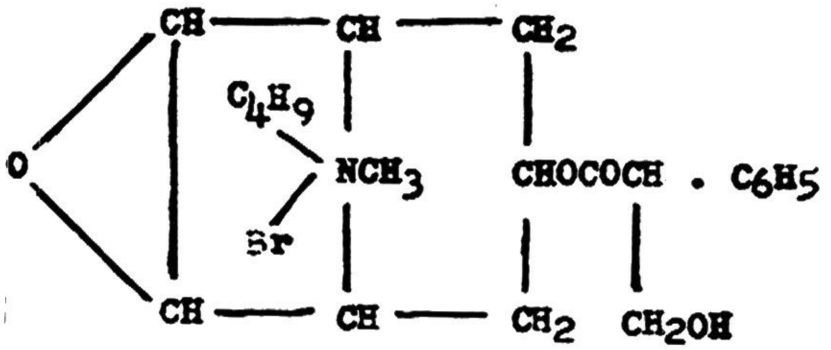
Hon. Commissioner of Patents
Washington, D. C.

Sir:

Responsive to the Examiner's letter of May 18th, 1953, please amend the application as follows:—

Cancel Claim 11.

Claim 10, line 2, after "C" insert—having the following structural formula:—



Cancel the title of the application and insert—Scopolamine-Bromobutylate and Process of Producing Same.—

## REMARKS.

The Examiner has rejected the claims as being unpatentable, over two (2) patents. Both of these patents had been discussed previously and the present invention differs completely from the prior art.

The Examiner is relying upon the patent to Merck who describes a homologue of applicant's compound. There is submitted herewith an affidavit of Dr. Wick which proves conclusively that the utility and the effectiveness of applicant's compound is entirely different from that of the patent. There is no analogy in the character of the effects obtained so that it is believed that the claims of the present application distinguish from this patent.

The Examiner also relies upon the patent to Scheuing and Krauss. Both of these patentees were employees of the assigneee of the present application and the invention of the patent was developed in the assignee's laboratories. Applicant has been unable to obtain affidavits from either of the patentees as the first is deceased, and the other is unavailable because he is in the Soviet zone of Germany. Therefore, there is being submitted herewith an affidavit of the present applicant which shows conclusively that the material of the patent is entirely different from the product claimed herein. It is impossible to obtain applicant's product by following the process of the patent and at no stage in the patent is applicant's compound formed.

The Examiner has rejected Claim 11 as not being proper product claim. In view thereof this claim has been cancelled and Claim 10 has been amended to give the structural formula.

It is believed that the present amendment together with the affidavit has demonstrated the novelty in the present invention and the unexpected result obtained therefrom, in view of which it is requested that the Claims be allowed.

Respectfully submitted,

*Attorney for Applicant.*

Paper No. 27

# DEPARTMENT OF COMMERCE

UNITED STATES PATENT OFFICE
WASHINGTON

Appeal No. 401 63
Before the Board of Appeals

In re application of Franz Adickes
Ser. No. 251,840
Filed Oct. 17, 1951
For Scopolamine-Bromobutylate and Process of Producing Same

Nelson Littell—*Attorney*

## EXAMINER'S STATEMENT

This is an appeal from the final rejection of claims 5-10, inclusive, 12 and 13. No claim has been allowed.

A correct copy of the appealed claims appears on pages 1 and 2 of applicant's brief.

The references of record relied on are:

| | | |
|---|---|---|
| Scheuing et al | 2,305,460 | Dec. 15, 1942 |
| Merck (German) | 145,996 | Nov. 2, 1903 |

The invention is believed to be adequately described in applicant's brief and by the appealed claims.

### *The References*

Scheuing et al disclose and claim (claim 8) the compound scopolamine bromobutylate.

Merck discloses the bromomethylate and bromethylate of scopolamine (page 1, lines 34-36) and disclose in Example 5 two alternative methods of producing the bromomethylate derivative, the first being by:

Mixing 100 g. of scopolamine (hyoscine) with an excess of methyl bromide in the absence of a solvent. The mass quickly solidifies to a solid crystaline cake. After having stood for two days, the reaction became neutral. Now again two liters of ether were added, then filtered and rinsed. Here also the yield is quantitative. After recrystallization from alcohol-ether, the white compound forms as small needles, easily soluble in water, difficulty soluble in cold alcohol, and insoluble in ether. It melts at 216 to 217° C. with decomposition.

the second being by:

Dissolving 100 g. of scopolamine in 400 g. of absolute alcohol and adding 60 g. of methyl bromide. After 48 hours, the reaction is terminated. The bromomethylate was mixed with 2 liters of ether and isolated and purified as in the preceding example.

Merck further teaches that alcohol, acetone, chloroform or other solvents may be used (page 2, lines 58-60).

### *The Rejections*

Claim 10, the only product claim now in the case, was rejected as unpatentable over Merck who teaches the bromomethylate and bromethylate derivatives of scopolamine, both of these compounds being lower homologues of applicant's claimed brombutylate. To overcome this rejection, an affidavit (Paper No. 8) by Dr. Wick was filed after final rejection purporting to show the nonanalogous pharmacological properties of the respective compounds. The affidavit is considered insufficient to overcome the rejection since no comparison can be found between the claimed brombutylate and the bromomethylate or bromethylate of the Merck patent. On pages 2 and 3 of the affidavit, methylscopolamine*nitrate* is compared with atropine derivatives and scopolaminehydrobromide, no butyl bromide quaternary salt being included; on page 4, the bromobutylate is compard with atropine and scopolamine, not the bromomethylate or bromoethylate of the Merick patent; the remainder of the affidavit is concerned with comparisons of the bromobutylate of the claim with atropine sulfate and scopolamine hydrobromide, not the bromomethylate or bromoethylate of the Merck patent. The affidavit is therefore thought to be insufficient to overcome the rejection on homology.

Claim 10 was further rejected as unpatentable over Scheuing et al who disclose applicant's compound. This rejection is believed to adequately treated in the Final Rejection.

Claims 5-9, inclusive, 12 and 13, the process claims, were rejected as unpatentable over Merck in view of Scheuing et al. Claim 12 which is the broadest process claim, save for the time limitation, claims a process which differs from that of Merck (Example 5b) only in that butyl bromide is substituted for the homologous methyl bromide and the time of reaction is extended from 48 hours to one month. No invention is seen in permitting a reaction mixture to sit until reaction is completed, especially in view of the fact that butyl bromide is known to be a less active quaternizing agent than is methyl bromide.

Other limitations found in some of the claims are not believed to be critical since they do not appear in all the process claims (In re Ripper, 80 USPQ 96) and furthermore, are disclosed in the instant specification to be equivalent conditions to those used by Merck (In re Borcherdt et al, 94 USPQ 175; In re Bloomer, 84 USPQ 135) i.e. the temperature limitation of 65° C. is disclosed as being detrimental in the last paragraph of page 4 of the specification, the acetonitrile solvent recited in some of the claims is stated to be equivalent to the chloroform, alcohol, and acetone of Merck on page 2, second paragraph, of the specification, etc.

For the above reasons the final rejection is thought to be proper.

Examiner

Levinson:cln
Nelson Littell
350 Madison Ave.
New York 17, N. Y.

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Paper No. 32

U. S. PATENT OFFICE
BOARD OF APPEALS

Appeal No. 401-63
Hearing: April 27, 1955

IN THE UNITED STATES PATENT OFFICE

BEFORE THE BOARD OF APPEALS

*Ex parte* Franz Adickes

Application for Patent filed October 17, 1951, Serial No. 251,840. Scopolamine-Bromobutylate and Process of Producing Same.

Nelson Littell for appellant

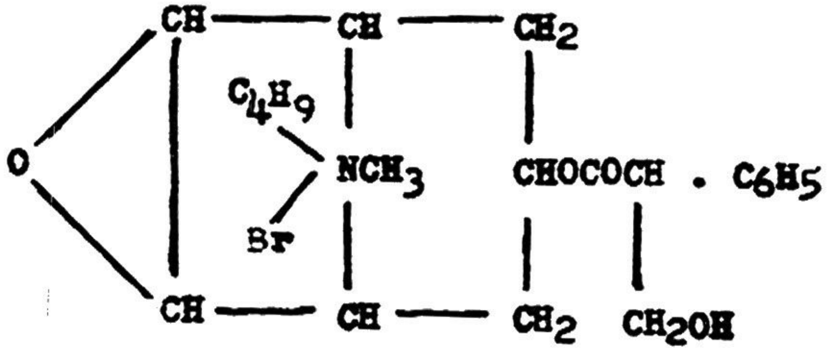
This is an appeal from the action of the Examiner finally rejecting claims 5 through 11, 12 and 13. Claim 11 was cancelled in an amendment subsequent to the final rejection. The appeal as to this claim will be dismissed.

Claims 5 and 10 are representative and read as follows:

5. A process for producing quaternary scopolamine-bromobutylate which comprises mixing scopolamine base with an excess of butyl bromide, dissolving said mixture in a solvent of strongly polar character, heating said solution to an elevated temperature up to about 65° C. but insuffi-

ciently high to cause decomposition to take place, dissolving the reaction product in an organic solvent, allowing said product to crystallize, and drying the product to remove residual solvent.

10. As a new product quaternary scopolamine-bromobutylate having a melting point of about 142° to 144° C. having the following structural formula:—



The references relied upon are:

| | | |
|---|---|---|
| Scheuing et al. | 2,305,460 | Dec. 15, 1942 |
| Merck (Ger.) | 145,996 | Nov. 2, 1903 |

Appealed claims 5 through 9, 12 and 13 are directed to a process of producing quaternary scopolamine-bromobutylate by reacting a scopolamine base with an excess of butyl bromide. In claims 5 through 9 the reaction is conducted at elevated temperatures up to about 65° C. In claims 12 and 13 the mixture is allowed to stand for at least one month to permit completion of the desired reaction. Claim 10 is to a quaternary scopolamine-bromobutylate having a melting point of about 142° C. This compound is alleged to have valuable therapeutic properties presumably as a spasmolytic. These properties will be referred to in more detail later in our decision.

Claim 10, to the product, stands rejected as unpatentable over Merck disclosing the bromomethylate and bromethylate derivatives of scopolamine. Both of these compounds are lower homologues of the claimed bromobutylate. Claim 10 was further rejected as unpatentable over Scheuing et al. who disclose and claim this compound (claim 8 of the patent). Process claims 5 through 9, 12 and 13 were rejected as unpatentable over Merck in view of Scheuing et al. Merck discloses the reaction of scopolamine with methyl bromide in alcohol or other polar solvent to form scopolamine-bromomethylate, dissolving the reaction mixture in alcohol, and crystallizing the product therefrom. The Examiner saw no invention in using Merck's method to produce the higher homologue, i.e., the scopolamine-bromobutylate of Scheuing et al. The latter produced the bromobutylate by reacting the scopolamine with crotonyl bromide followed by hydrogenation.

Appellant's arguments for patentability of the foregoing claims are essentially (1) the method of the Merck patent will not produce scopolamine-bromobutylate, (2) although it is admitted that Merck's compounds are lower homologues, appellant believes the bromobutylate possesses sufficiently distinctive and unexpected properties to be patentable over these homologues under the *In re* Hass et al. doctrine, 31 C.C.P.A. 895; 1944 C.D. 234; 563 O.G. 576; 141 F. (2d) 122; 60 USPQ 544, (3) the Scheuing et al. patent did not, in fact, produce scopolamine-bromobutylate but merely the old and well known scopolamine-hydrobromide; further that claim 10 in any event distinguishes from Scheuing et al. in the designated melting point.

Appellant's first enumerated argument is supported by an affidavit Oct. 29, 1953 which reports an attempt to produce scopolamine-bromobutylate by reacting scopolamine with n-butyl bromide in conformity with the procedure of Merck. Even after allowing the mixture to stand four days instead of two days, as mentioned in Merck, no reaction took place. Furthermore the scopolamine base was unchanged after six days. These experiments are relied on to show that the Merck process was not suitable for production of scopolamine-bromobutylate. Appellant made the procedure operative by either allowing a long reaction time of the order of at least one month or by heating under reflux at temperatures at 65° for approximately seven days. The argument suggests that use of a strong polar solvent such as acetonitrile may be the key to appellant's success where others failed. The allegedly drastic conditions of the reaction are said to involve sufficient departure from Merck to constitute an inventive advance thereover.

We have considered the arguments falling under this heading (1) but are not convinced that the Examiner erred in his conclusion that no invention is involved in permitting the reaction mixture to set until the reaction is completed, especially in view of the fact that butyl bromide is known to be a less active quaternizing agent than methyl bromide. We believe chemists are well aware that heating a reaction mixture will shorten the time required to complete the reaction. In lieu of the heating a longer time must be utilized and this is all that is represented by claims 12 and 13. We are therefore not convinced that appellant made any invention over the Merck process merely by substituting butyl bromide for ethyl or methyl bromide. Furthermore, Merck, page 1, line 28, mentioned the use of alkyl bromides generally for reaction with the scopolamine. On the point of using a strong polar solvent, we fail to see any distinction whatever from Merck who discloses alcohol, acetone and chloroform for this purpose. These are the same polar solvents named by appellant on page 2 of his specification.

The second main argument for patentability (2) is based on alleged superiority of the bromobutylate over the homologue bromomethylate. The specification, as well as the affidavits of Dr. Wick, compare the claimed scopolamine bromobutylate with scopolamine and atropine which makes it necessary to briefly refer to the essential characteristics of these two drugs.

Atropine exhibits many complex pharmacological activities but the two main actions are (a) stimulation of certain medullary and higher nerve centers (b) paralysis of secretory glands and the smooth muscle fibers innervated by the para-sympathetic division of the autonomic nervous system. In addition atropine exerts an effect on the smooth muscle of gall bladder and biliary ducts as well as on smooth muscle of viscera supplied by the sacral parasympathetic ganglia. Scopolamine is a paralyzant to the peripheral ends of the parasympathetic nerves acting precisely like atropine although less powerfully. By virtue of this action it dilates the pupil, causes dryness of throat and skin and accelerates heart action. It differs strikingly from atropine in that it is not a stimulant to the medullary centers and therefore does not increase respiration or elevate blood pressure.

The specification is not too clear on the intended application of the scopolamine-bromobutylate. On page 3 after referring to the much lower mydriatic activity of this compound as compared with scopolamine and atropine appellant states:

> "By reason of this advantageous property as well as the fact that with scopolamine-bromobutylate the action on the heart amounts to only 1/30th that of atropine, whilst the action on the stomach, gut and gall bladder is about equal to that of atropine and the far-reaching non-toxicity, scopolamine-bromobutylate has a very extra-ordinary importance as a spasmolytic."

With the above in mind we will consider the affidavits of Dr. Wick which are relied on to establish superior pharmacological properties for the scopolamine-bromobutylate as compared with the bromomethylate and certain atropine derivatives. The main differences stated to be established by the first Wick affidavit are the markedly lower activity in acceleration of pulse (30 times smaller), mydriasis (500 times smaller), inhibition of saliva secretion (50 times smaller) and reduction of tonicity of the isolated intestine treated with acetylcholin (100-150 times smaller). The conclusion sought to be drawn is that making scopolamine quaternary by n-butyl produces an entirely novel pharmacological item whose special effect could not be predicted. The Examiner found this affidavit insufficient to establish non-analogous and superior pharmacological properties in the brombutylate largely because no comparison was made between the brombutylate and the bromomethylate or bromethylate of the Merck patent. In a subsequent affidavit by Dr. Wick filed April 5, 1954 and reviewed in the Reply Brief, it is asserted that the methyl-scopolamine-nitrate, which was mentioned in the first Wick affidavit, is, in fact, the full equivalent of the methyl-scopolamine-bromide. Even if this be assumed to be correct, and we have no real reason for doubting it, the first affidavit would still be insufficient to establish superiority in appellant's compound.

Pages 2 and 3 of the first Wick affidavit refers to some published experiments by Nyman involving comparisons of the properties of methyl-scopolamine-nitrate, scopolamine hydrobromide and certain atropine derivatives, such as the sulfate. This comparisons fails because no comparison is made with the presently claimed scopolamine-bromobutylate. On page 4 of the first Wick affidavit a bromobutylate is compared with atropine and scopolamine but not the bromomethylate or bromoethylate of the Merck patent. The affidavit further compares the bromobutylate of the claims with atropine sulfate and scopolamine hydrobromide again failing to make a direct comparison with the lower homologues of Merck. The law is clear that a direct comparison with the closest prior art is required under these circumstances. *In re* Renstrom, 36 C.C.P.A. 1020; 1949 C.D. 306; 624 O.G. 5; 174 F. (2d) 140; 81 USPQ 390.

The second Wick affidavit seeks to correct the defect by equating methyl-scopolamine-nitrate (which is several times more powerful than atropine) to methyl-scopolamine-bromide and further by stating that if the scopolamine-bromobutylate claimed is tested in a manner similar to that reported by Nyman certain results are obtained. In general these are to the effect that the spasmolytic action, mydriasis, salivary action, and acceleration of the heartbeat is considerably less than that of atropine (considered as standard). In particular the second Wick affidavit states:

> "scopolamine-bromobutylate is only from 1/100 to 2/1000 as powerful as atropine in the tested spasmolytic effect . . ."

We are unable to reconcile the last quoted portion with the statement in the original specification to the effect that the scopolamine-bromobutylate is about equal to atropine in this effect. If the affidavit is correct we fail to see how appellant's compound could ever be a drug of choice in place of atropine for relieving muscular spasms. The vast reduction in physiological activity on all fronts (as compared with atropine) leads one to inquire whether or not appellant has a drug of any significant utility. To establish this requires clinical data of tests conducted on humans. The Wick affidavits may be regarded as the usual preliminary and routine pharmacological tests conducted on animals. Such tests are of course necessary but do not establish the ultimate value of any drug.

It is our conclusion that the data submitted is insufficient to establish superiority of the claimed compound over the corresponding lower homologues of the Merck patent.

The third main point in the argument, namely, that Scheuing et al. did not obtain scopolamine-bromobutylate and that, in any event, claim 10 distinguishes by virtue of the lower melting point is without validity. The law is clear that the disclosure of a product in a publication is sufficient to anticipate a claim therefore and the operativeness of the process by which it is produced is completely

immaterial. *In re* Von Bramer et al., 29 C.C.P.A. 1018; 1942 C.D. 462; 542 O.G. 183; 127 F. (2d) 149; *In re* Crosley et al., 34 C.C.P.A. 882; 1947 C.D. 216; 600 O.G. 172; 159 F. (2d) 735; 72 USPQ 499; Merck v. Marzall, 1952 C.D. 35; 661 O.G. 576; 197 F. (2d) 206; 93 USPQ 355; *In re* Kebrich 40 C.C.P.A. (Pats.) 780; 1953 C.D. 94; 671 O.G. 597; 201 F. (2d) 951; 96 USPQ 411. Scheuing et al. sought to produce scopolamine-bromobutylate and proceeded to claim it. The fact that they may not have obtained it is immaterial. Such disclosures suffice to anticipate claims to that compound and the fact that appellant seeks to introduce an additional distinction in the lower melting point is of no avail. The scopolamine-bromobutylate of Scheuing et al. would have been a reference under the law whether or not any of its properties were disclosed. Appellant is therefore not in any better position merely because he gives one of the physical characteristics of the compound. We are satisfied that there is no error in the rejection of claim 10 on Scheuing et al.

Since the arguments and showings of record do not convince us of any error in the position taken by the Examiner, his rejection of all the claims on the grounds stated will be sustained.

The appeal as to claim 11 is dismissed.

The decision of the Examiner is affirmed.

Board of Appeals
C. S. Duncombe
*Examiner-in-Chief*
N. A. Asp
*Examiner-in-Chief*
G. P. Sakis
*Examiner-in-Chief*
(*Acting*)

May 16, 1955

Nelson Littell
350 Madison Ave.
New York 17, N. Y.

**Plaintiff's Exhibit No. 3**

Scopolamine Methylbromide. Scopolamine methylbromide (*methscopolamine bromide, pamine bromide, epoxymethamine bromide*) is the N-methylbromide (quaternary ammonium derivative) of scopolamine (Tables 25, 26). Its pharmacological properties in animals and in man were described by Nyman (1943 *et seq.*), and subsequently by Visscher and co-workers (1954), Kirsner and co-workers (1954), and others. The drug is available in 2.5-mgm oral tablets. The average adult dose is 2.5 mgm three times daily before meals and at bedtime. The *pharmacological* anticholinergic atropine-like drugs, but the compound lacks *properties* of scopolamine methylbromide are typical of the central nervous system actions of scopolamine. It appears to be as active as atropine against methacholine-induced vasodepression and spasm of smooth muscle, but its duration of action is more prolonged. The drug diminishes gastric secretion and gastrointestinal motility. Side effects in man include dry mouth, blurred vision, constipation, and urinary retention. The drug has been proposed for the adjunct therapy of peptic ulcer, gastrointestinal hypermotility states, postgastrectomy "dumping" syndrome, hyperhidrosis, sialorrhea, and ureteral and vesical spasm. The ultimate value of scopolamine methylbromide will not be known until considerably more clinical experience has been gained in its use. The drug is not official and is not described in N.N.R.

Scopolamine Butylbromide. This compound (scopolamine-N-bromobutylate, *buscopan*) is the N-butylbromide (quaternary ammonium) derivative of scopolamine. The drug exhibits to a mild extent the anticholinergic and spasmolytic actions of atropine, but possesses rather marked ganglionic blocking and curariform properties (*see* Wick, 1951; Philippot and Dallemagne, 1953). The compound lacks the central stimulant action of atropine. It has had preliminary therapeutic trial in gastrointestinal disorders. The drug is not generally available and considerably more experience will be necessary to determine its clinical value.

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**Plaintiff's Exhibit No. 4**

Translation of Summary of Articles from Arch. exper. Path. u. Pharmakol., Vol. 213, pp. 485-500 (1951)

### PHARMACOLOGY OF BUSCOPAN

by

Helmut Wick

*Summary*

1. A series of 9 quaternary ammonium compounds of scopolamine were investigated with respect to spasmolysis, cardiac accelerating effect, mydriasis, effect on central nervous system and toxicity in comparison with atropine. The N-butyl compound (Buscopan) was marked by a good spasmodic action (1/2 to 1 atropine), absence of scopolamine stimulation on the central nervous system, low pupil dilating effect (1/500 of atropine) and low toxicity. The pulse acceleration is 30 times less than after atropine, the reduction in saliva secretion in cats is 50 times less than after atropine, while the bronchial dilating effect of spasms in the dog induced by pilocarpine is equal to that of adrenalin but of longer duration.

2. A more detailed investigation of Buscopan was that it is a compound which is not active against muscarine-like effects of acetylcholine but against the nicotine-like ganglionic stimulating effects of acetylcholine. For example, the spasms of an isolated intestine induced by pilocarpine are eliminated by almost the same dosage as that of atropine, in the increase of tone of the intestine by small dosages of acetylcholine it is about 100-500 times weaker than atropine. The cholinergic blood pressure increase as well as the effects produced by electrical stimulation of the vagus on the intestine can be suppressed by Buscopan.

3. Buscopan has strong antinicotinic properties and can be regarded as a ganglionic blocking agent. It does not have any substantial similarity with the atropine scopolamine group and belongs, pharmacologically speaking, into the class of tetraethylammonium, but exceeds this compound with reference to its effect upon the vagal system as well as with reference to the absolute effective dose.

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**Plaintiff's Exhibit No. 5**

## PHARMACOLOGY OF PAMINE BROMIDE

F. E. Visscher, P. H. Seay, A. P. Tazelaar, Jr.,
W. Veldkamp and M. J. Vander Brook

*The Upjohn Company, Department of Pharmacology.*
*Kalamazoo, Mich.*

J. Pharmacol. 188, 198, 199-200

Received for publication September 8, 1953

Other actions. *Mydriatic activity in rabbits.* Topical application of Pamine bromide was employed to determine mydriatic action in rabbits. The drug (0.1 to 0.2 ml. of a dilute solution) was instilled into the conjunctival sac and washed out 30 seconds later. The eyes were illuminated with a triple bulb fluorescent light 25 cm. over the rabbit's head. The diameter of the pupil was estimated with the aid of a caliper ruler. As shown in table 6 Pamine bromide by local application was much more potent than atropine sulfate or homatropine hydrobromide. A maximum effect was noted with Pamine bromide 30 minutes after dosage.

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The potency of Nyman's scopolamine N-methyl bromide in the reduction of pilocarpine stimulated salivation in man was found to be about 0.8 times that of scopolamine hydrobromide and 2.4 times that of atropine sulfate (Nyman, 1943). We found the antisialogogue potency of Pamine bromide in pilocarpine stimulated rabbits to be 4.0 times that of atropine sulfate.

The mydriatic activity of Nyman's compound in man by local application was found to be equivalent to scopolamine hydrobromide (Nyman, 1943). He had reported earlier (1942, p. 68) that scopolamine hydrobromide was about 2.9 times as effective as atropine sulfate as a mydriatic in man. We have found (table 6) that Pamine bromide is about 45 times as effective as atropine sulfate on local application to the rabbit cornea.

Nyman (1943) also reported that, on subcutaneous injection into man of 0.3 mgm. of his scopolamine N-methyl bromide, the heart rate was increased by an average of 39 per cent in ten subjects, while scopolamine hydrobromide was without effect. Contrary to his findings at lower dosage, Nyman (1943) found in a single human subject no noticeable cardioacceleration after the subcutaneous injection of 0.9 mgm. of his scopolamine N-methyl bromide. Kirsner (1953) in clinical trials has observed no increase in average heart rate after parenteral doses up to 0.3 mgm. of Pamine bromide. Contrary to Kirsner's observations in human subjects, we found that Pamine bromide increases the heart rate in dogs after both intravenous and intramuscular administration.

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**Plaintiff's Exhibit No. 6**

## N-METHYLATED SCOPOLAMINE DERIVATIVES

Acta Physiol. Scand. *6*, pages 260-265

*Page 2*

With reference to details of the method as well as basis for calculation of the relative strength of the secretion-reducing substances in comparison to SHB, attention is directed to the author's prior work (1942).

The results are shown in Fig. 1. Very similar results were obtained with the other test subject. The relative strength of the new substance as compared to SHB with respect to saliva secretion induced in one parotis gland by pilocarpine are as follows:

| Substance | Test Subject E | Test Subject O | Average Value |
|---|---|---|---|
| Methyl-scopolamine nitrate | 0.071 | 0.065 | 0.07 |
| Scopolamine hydrobromide | 0.059 | 0.062 | 0.06 |
| Methyl-scopolamine bromide | 0.042 | 0.051 | 0.06 |

*Page 3*

Therefore, the relative strength values with respect to reduction of saliva secretion are 1.2 for MSN and 0.8 for MSB, if SHB is given a value of 1. If a comparison is made with atropine-sulfate, the respective values are 3.6 and 2.4, respectively. Methyl-scopolamine nitrate is therefore the strongest of all heretofore known saliva-secretion-reducing pharmaceuticals.

The mydriatic effect of the new substances was tested by the method previously used (1942) by the author, that is with the Hass pupiloscope by determination of the differential sensitivity with respect to motility of the pupils. In two test subjects, the mydriatic effect for both substances was practically the same and equally as great and of the same duration as the effect of SHB.

*Page 4*

The results are shown in the following table which indicates that SHB produces the greatest deviation from the pulse rate at rest, and that the other compounds produced the highest observed pulse rate presented in per cent of the initial value.

The old observation that SHB does not affect the cardiac vagus noticeably in therapeutically useable doses is therefore clearly substantiated, and at the same time it was found that the N-methylated scopolamine derivatives retain the characteristic property of the active group of atropines, that is to reduce the effect of the cardiac vagus. The effect is very marked, and even though the difference between the nitrate and the bromide is not statistically certain, the tendency is nevertheless present, that is, the nitrate also exhibits a stronger effect in this respect than the bromide.

*Page 6*

Systematic investigations of two new N-methylated scopolamine derivatives, MSN and MSB, are reported. As a saliva secretion reducing agent, the first is stronger than SHB, and therefore the strongest known compound in this respect. The mydriatic effect corresponds by and large to that of SHB. In contrast to the parent compound, the two derivatives have a marked influence on the vagus of the heart in human beings. It is shown that the property of SHB upon which the sedative effect of this compound on the central nervous system of human beings is based is eliminated in the new derivatives. The toxicity in mice is increased to about three times.

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**Plaintiff's Exhibit No. 7**

## EFFECTS OF A NEW CHOLINERGIC BLOCKING AGENT (SKF-1637) ON GASTRIC MOTOR AND SECRETORY ACTIVITY*

By E. Clinton Texter, Jr., M.D. et al

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Conclusions. 1. SKF-1637 (scopolamine-n-bromobutylate) exerts a profound cholinergic blocking effect upon both gastrointestinal motility and gastric secretion.

2. This drug administered parenterally is highly effective in relieving ulcer pain.

3. Side effects are absent or minimal following its use.

4. The role of this drug in the long-term management of peptic ulcer is yet to be determined.

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**Plaintiff's Exhibit No. 8**

## COMPARATIVE EXPERIMENTAL STUDIES ON THE ACTION OF SPASMOLYTICS AND GANGLIONIC BLOCKING AGENTS (ATROPINE, AVACAN, PENDIOMID, BUSCOPAN, BANTHINE) ON THE MOTILITY OF THE SMALL INTESTINE IN MAN

Zeitschrift fuer die gesamte experimentelle Medizin, Vol. 120, No. 6, pages 599-612 (1953)

*Page 20*

Pendiomid and Buscopan are, as far as their action on the motility of the small intestine is concerned, superior and, as far as duration is concerned, equal to atropine in large doses. Pendiomid in large amounts may cause collapse. Buscopan has no disturbing side-effects.

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**Plaintiff's Exhibit No. 9**

## EXPERIMENTAL STUDIES REGARDING THE BLADDER TONUS

Zeitschrift fuer urologie, Vol. 46, No. 7,
pages 456-466 (1953)

*Page 18*

In addition the influence of so-called ganglionic blocking agents (Buscopan, Pendiomid) on the bladder musculature was studied. Buscopan induces favorable sedation especially of the spastic bladder while Pendiomid shows a more pronounced effect on the blood pressure and alters the bladder tonus but slightly.

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**Plaintiff's Exhibit No. 10**

## ON THE INFLUENCE OF THE VAGOTROPIC GANGLIONIC BLOCKER BUSCOPAN DURING THE PERIOD OF DILATATION

Deutsches Medizinisches Journal, Vol. 3,
No. 15/16, pages 336-338 (August 15, 1952)

*Page 8*

Summing up, it can be stated that Buscopan represents a drug which is free of side-effects and exerts a remarkable accelerating effect on the process of dilatation and intensifies the activity of labor pains. The preparation is in every respect harmless to mother and baby.

The most favorable moment for its administration is when the os uteri has an opening size of a 5 Mark piece, provided regular activity of labor pains takes place. The doses may be repeated without hesitation after a brief interval. As there is no analgesic effect, anesthesia with nitrous oxide or Trichloran should be considered. No unfavorable effects as to expulsion period and placental stage were observed.

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**Plaintiff's Exhibit No. 11**

## ON THE EFFECTIVENESS OF DRUG THERAPY IN GASTRIC AND DUODENAL ULCER

German Medical Journal, Berlin, August 15, 1953,
pages 409 to 411, No. 15/16

*Page 6*

D. While the patients receiving no medication were generally free of pain during the first days only for a while after application of heat, the patients given Buscopan felt markedly better during the entire day.

E. Buscopan showed good results also in recurrent ulcers, contrary to the findings of another worker, who found results primarily in fresh ulcers.

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**Plaintiff's Exhibit No. 13**

## EFFECTS OF BUSCOPAN IN GASTRIC AND INTESTINAL SPASM

Medical Clinic, No. 4 (January 25, 1952), pages 121-124

*Page 6*

. . . intravenous administration of Buscopan induced spasmolysis in a few minutes *time,* without significant side effect . . .

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**Plaintiff's Exhibit No. 14**

## ADMINISTRATION OF BUSCOPAN IN SPASMODIC DISORDERS

German Medical Weekly, July 18, 1952, No. 29/30,
pages 906-909

*Page 16*

Undesirable side effects such as usually occur with medications in the atropine series have never been observed with Buscopan, even in high dosages.

We believe that Buscopan represents a valuable addition to the armamentarium for the management of spasmodic conditions of the widest variety of origins.

Plaintiff's Exhibit No. 15

## A CONTRIBUTION TO ESOPHAGEAL DIAGNOSTICS

The Medical Journal, March 27, 1954, No. 13

*Page 12*

Esophageal disorders have been described in which the problem to be clarified was to the degree the changes found represented purely spasmodic or purely organic conditions, or combinations of both. Intravenous application of the spasmolytic Buscopan made it possible in a few minutes time, and without disturbing side-effects, to alleviate spastic states to a degree sufficient to differentiate spasmodic changes from organic changes in the esophagus and cardia.

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Plaintiff's Exhibit No. 16

## THE ROLE OF FUNCTIONAL, SPASTIC MUSCLE CONTRACTIONS IN THE ETIOLOGY OF THE CASCADE STOMACH

Fortschritte Röntgenstr. 78:49, 1953

*Page 3*

In conclusion the author emphasizes that despite the high dose of Buscopan only 4 patients, if specifically asked, indicated slight dryness of the mouth and weakness of accommodation for a short period.

**Plaintiff's Exhibit No. 17**

## ON THE ACTION OF HYOSCINE-n-BUTYLBROMIDE (BUSCOPAN) ON THE MOTILITY OF THE GALL BLADDER

Klinische Medizin, Vol. 9 (1954), pages 74 to 79

*Page 10*

Thus, Buscopan offers the means to more readily recognized functional disorders of the biliary duct system and to favorably affect such disorders by causal therapy.

*Page 10, continued on Page 11*

The action of hyoscine-n-butylbromide (Buscopan) on the motility of the muscular structure of the gallbladder can be promptly abolished by Buscopan and that the gallbladder reflex is also blocked by the effect of this drug. In addition to the clinically tested favorable action on various gallbladder affections by means of Buscopan, it is particularly pointed out its special effect on dyskinesias. The results are demonstrated by X-ray pictures.

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**Plaintiff's Exhibit No. 18**

## CLINICAL EXPERIENCES IN OBSTETRICS WITH THE SPASMOLYTIC AGENT "BUSCOPAN"

Aerztliche Wochenschrift, Vol. 8, No. 50, 1953,
pages 1203-1204

*Page 4*

Buscopan is a drug available to the obstetrician, which shortens the first stage of labor in primiparae and multiparae without causing undesirable side-effects for either mother or child. It furthermore affects uterine contractions indirectly in a favorable way and can be used even in large doses in normal as well as in complicated cases of labor.

**Plaintiff's Exhibit No. 19**

## SPASMOLYTIC ACTION OF THE VAGOTROPIC GANGLIONIC BLOCKING AGENT BUSCOPAN IN SALPINGO-SPASM

Zentralblatt fuer Gynaekologie, Vol. 76, page 894 (1954)

*Page 6*

For these reasons the author recommends the use of Buscopan orally during the first half of the menstrual cycle in cases of "childlessness without cause", especially if during testing of tubal patency spasms occur. In addition and at the same time estrogens may also be administered.

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**Plaintiff's Exhibit No. 20**

## IMPROVEMENT OF X-RAY DIAGNOSIS OF THE URINARY TRACT BY GANGLIONIC BLOCKING AGENTS

Deutsche Medizinische Wochenschrift, 79:1169-1171, 1954

*Page 10, Continued on Page 11*

Studies involving pyelography, urethro-cystography, and moving pictures were performed to test pharmacological vagotropic ganglionic blocking in the urinary tract.

In 190 excretory and 98 retrograde pyelograms, 30 mgm of Buscopan was given i.v. during the study because of inadequate or incomplete filling of the renal pelvis, narrowing of the pelvic calyx system, narrow necks of the calyces, vague papillary impressions or poor visualization of the ureters. Improved visualization of the renal pelvis, or, respectively, of the ureters, or release of spasm was observed in 128 i.v. and 62 retrograde pyelograms after 3 to 5 minutes.

**Plaintiff's Exhibit No. 21**

## THE EFFECT OF BUSCOPAN ON RENAL PRESSURE

Die Medizinische, June 6, 1953, No. 23

*Page 5, Continued on Page 6*

As a ganglionic blocking agent, Buscopan has an excellent effect in combatting spastic conditions. The great number of publications renders discussion of the different indications superfluous.

Our own clinical experiences are based upon 250 cases with urological disease. In addition renal pressure measurements were performed to supplement the results already available from animal and clinical experiments. The method which we have previously used to test other therapeutic agents, is presented and the technical aspects of the experiments are discussed more in detail. Buscopan is undoubtedly responsible for a marked decrease of pressure in the kidneys and simultaneous prolongation of the interval between individual contractions. The change in tonus and rhythm illustrated by means of 8 figures, proves the clinical results. The rapidly occurring measurable effect of Buscopan which appears within the first minute after injection, should be emphasized.

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**Plaintiff's Exhibit No. 22**

EXHIBIT B

| | Atropine | Scopolamine Bromomethylate | Scopolamine Bromo-butylate |
|---|---|---|---|
| Inhibition of Saliva | 1.0 | (1) 3.6 | (3) 0.05 |
| Cardiac Acceleration | 1.0 | (2) 4 to 5 | (3) 0.033 |
| Pupil Distention | 1.0 | (1) 3.0 | (3) 0.002* |

Authority
- (1) Nyman
- (2) Wick testimony
- (3) Wick—Pharmacology of Buscopan

**Plaintiff's Exhibit No. 23**

## TRANSLATION
## IMPERIAL PATENT OFFICE

German Patent No. 145,996

Class 12 p

Issued: November 2, 1903

Firm E. Merck of Darmstadt

## Process of Producing Bromo Methylates and Bromo Ethylates of Alkaloids of the Tropeine and Scopoleine Group

Patented in the German Reich from September 27, 1902 on

According to Fraenckel "Arzneimittelsynthese"/Synthesis of drugs/1901, page 222, the salts of methyl and ethyl atropine are said to have a lethal effect in much smaller doses than salts of atropine itself. Recent research work, however, has shown that, in contrast thereto, atropine methyl bromide is less toxic than atropine salts themselves (Vaubel "Wochenschrift fuer Therapie und Hygiene des Auges" vol. 6, # 2 and Darier "Chimique Ophthalmologique 1902, 8th year, # 21, p. 318).

Investigation of bromides of similar derivatives of other alkaloids of the tropeine and scopoleine group has furthermore shown that said compounds are favorably distinguished also over the original alkaloids since they are entirely free of undesired side-effects or since such side effects at least strongly recede while the desired properties of said plant bases are preserved.

Said bromides have the further remarkable advantage that they crystallize very readily and in good form and can be produced in a very convenient manner directly from the alkaloids by the action of the corresponding alkyl bromides. It is only necessary to bring together at ordinary temperature the alkaloids or their solutions, respectively, with said alkyl bromides in the required amount or in a slight excess in order to obtain, after a short period of time, said compounds in crystalline form and with a quantitative yield. Up till now there have been produced in this manner and have been tested the bromo methylates and bromo ethylates of the following tropeines and scopoleines.

*Examples*

1. Hyoscyamine bromo methylate.

100 g. of hyoscyamine of highest purity are dissolved in 500 g. of ethanol or chloroform and 50 g. of methyl bromide are added thereto. After allowing the mixture to stand at ordinary temperature in a closed container for 20 hours, its alkaline reaction has disappeared. 2000 cc. of ether are added whereby the bromine salt is precipitated, filtered off by suction, and washed with ether. The yield corresponds to the theoretical yield. The compound forms colorless crystals and is readily soluble in water, difficultly soluble in cold, absolute ethanol, insoluble in ether. Melting point: 210-212° C.

2. Atropine bromo methylate.

120 g. of atropine of highest purity are dissolved in 500 g. of absolute ethanol and 75 g. of methyl bromide are added. After allowing the mixture to stand for 16 hours at ordinary temperature in a well closed container, it has attained neutral reaction. A large quantity of either is added and the resulting precipitate is filtered off by suction. The yield corresponds to the theoretical yield (159 g.). The compound is finally recrystallized from hot alcohol and is obtained thereby in white, glittering flakes which are readily soluble in water, difficultly soluble in cold ethanol, readily soluble in hot ethanol, and insoluble in ether. Melting point: 222-223° C.

3. Atropine bromo ethylate.

50 g. of atropine of highest purity are dissolved in 200 g. of acetone and 40 g. of ethyl bromide are added thereto. After allowing the mixture to stand for some time, the bromo ethylate precipitates in crystalline form. It is worked up in the same manner as described for the methyl compound. The compound forms crystals melting at 173-174° C. which are readily soluble in water and ethanol.

4. Homatropine bromo methylate.

50 g. of homatropine are dissolved in 500 cc. of absolute ethanol and 30 g. of methyl bromide are added thereto. The mixture is allowed to stand at room temperature in a closed container. The alkaline reaction has disappeared after 3 hours. The mixture is concentrated by evaporation at a moderate temperature and the precipitated mass is recrystallized from alcohol-ether or acetone-ether. Colorless crystals are obtained in this manner. Said crystals are readily soluble in water, fairly soluble in absolute alcohol, insoluble in ether. Melting point: 180-181° C. When using acetone, in place of absolute ethanol, as solvent for homatropine, homatropine bromo methylate crystallizes for the most part very rapidly.

5. Scopolamine bromo methylate.

a) An excess of methyl bromide is added, without addition of a solvent to 100 g. of scopolamine (hyoscine). The mass very rapidly solidifies to a solid crystal cake. After standing for 2 days, the reaction has become neutral. 2 liters of ether are also added, the precipitate is filtered off by suction and is washed. In this case the yield is also quantitative. The compound, after recrystallization from ethanol-ether, forms white small needles which are readily soluble in water, difficultly soluble in cold ethanol, insoluble in ether. It melts at 210-217° C. thereby decomposing.

b) 100 g. of scopolamine are dissolved in 400 g. of absolute ethanol and 60 g. of methyl bromide are added thereto. The reaction is completed after 48 hours. 2 liters of ether are added to the bromo methylate which is isolated and purified as described in the preceding example.

### *Patent Claim*

Process of producing the bromo methylates and the bromo ethylates of alkaloids of the tropeine and scopoleine group by reacting methyl or ethyl bromide at ordinary temperature with the free alkaloids or their solutions in ethanol, acetone, chloroform or the like solvents, respectively.

**Patented Dec. 15, 1942** **Plaintiff's Exhibit No. 24** **2,305,460**

# UNITED STATES PATENT OFFICE

**2,305,460**

## QUATERNARY SALTS OF SCOPOLAMINE AND PROCESS FOR THEIR PRODUCTION

Georg Scheuing and Wilhelm Krauss, Ingelheim-on-the-Rhine, Germany; vested in the Alien Property Custodian

No Drawing. Application April 23, 1940, Serial No. 331,128. In Germany May 25, 1939

9 Claims. (Cl. 260—292)

This invention relates to new quarternary salts of scopolamine and a process of producing the same.

As known, methyl atropinium nitrate has a stronger although less prolonged an action than atropine. The proportion of the activities of both these substances amounts to about 2:1. The higher homologues, as the n-butyl or n-propylatropinium salts are practically as active as the methyl compound.

It has been found that the methyl scopolaminium salts have stronger action than scopolamine, the increase in the activity amounting to about the twofold. It is surprising that the action of the higher homologues differs from that of the atropine and amounts to the manifold of the action of scopolamine itself. So for instance n-propylscopolaminium bromide, when introduced subcutaneously has, measured at the mouse eye a 40-times, and the n-butylscopolaminium salt, measured at the rabbit eye—a 10-times as strong an action as scopolamine.

The above named higher quarternary salts cannot be easily obtained in the usual way by reacting the corresponding alkylesters with highly strong acids and the base, as the capability of reacting of these higher alkylesters is not great enough for producing an addition compound without danger of racemisation or another decomposition. On the contrary, allylesters, such as crotonyl bromide, are able to form addition compounds with scopolamine in the shortest time at room temperature.

According to the invention, the production of quarternary salts of scopolamine is therefore based on the addition of unsaturated alkylesters of strong acids, such as allyl or crotonylester to the free base, the obtained quarternary salt, containing the unsaturated alkyl groups, being then converted into the saturated compounds by usual reduction, for instance by catalytic hydrogenation. As esters of strong acids may be named the esters of halogen hydracids, sulphuric acid, sulphonic acids, such as benzene or toluene sulphonic acid and the like.

When carrying out the process according to the invention, the scopolamine is dissolved in organic solvents, such as alcohol, benzene, chloroform and the like and the solution mixed with the corresponding allyl or crotonylester The quantities of scopolamine and ester should correspond to the proportion of 1:1, but an excess in ester may also be used. The reduction of the quarternary scopolamine compounds, containing unsaturated alkyl groups, takes place by way of the catalytic hydrogenation, using the normal catalysts for hydrogenation, such as platinum, palladium, nickel or copper. The corresponding compounds are dissolved in the usual solvents, such as methyl alcohol, aqueous ethyl alcohol or glacial acetic acid.

In the following the process, according to the invention, may be explained on the basis of some examples, no limitation of the invention to the initial materials, proportions of their quantities, temperatures, etc., as stated in the examples, being intended.

### *Example 1*

28 parts of scopolamine purum are dissolved in 100 cc. of alcohol and 28 cc. of crotonyl bromide added. After some time crystallisation takes place. 24 hours later the scopolamine bromcrotonylate is sucked off, washed and dried. Melting point: 98° C.; yield: 88%.

35 parts of scopolamine bromcrotonylate are dissolved in methyl alcohol, 5 grs. of 10% palladium charcoal added and treated with hydrogen at room temperature. The hydrogenation is finished as soon as 1 mol. of hydrogen is taken up. The catalyst is sucked off, the solvent as far as possible distilled off and the scopolamine brombutylate formed precipitated with ether. Melting point: 195–197° C.; yield: 78%.

### *Example 2*

6.6 grs. of scopolamine are dissolved in 12 cc. of absolute methyl alcohol and 6 cc. of allyl bromide added. The solution is allowed to stand during 24 hours at room temperature and ether is then added until the liquid becomes turbid, after which the scopolamine bromallylate crystallises out. Yield: 9 grs.; melting point under decomposition at 165–166° C.

14 grs. of scopolamine bromallylate are dissolved in 150 cc. of methyl alcohol, 5 grs. of 10% palladium charcoal added and treated with hydrogen, 1 mol. of the latter being taken up. The filtrate is concentrated and the scopolamine brompropylate formed is precipitated with ether. Yield: 12 grs.; melting point: 194° C.

We claim:

1. Process for the production of quarternary salts of scopolamine, consisting in the addition of unsaturated alkylesters of strong acids to scopolamine and in the catalytic hydrogenation of the compounds formed, said unsaturated alkyl compounds having the following structural formula:

$$R{=}CH{-}CH_2X$$

wherein R is a hydrocarbon radical having from 1 to 2 carbon atoms, and X is the radical of a strong acid.

2. Process as specified in claim 1, consisting in the addition of allylesters of strong acids to scopolamine.

3. Process as specified in claim 1, consisting in the addition of crotonylesters of strong acids to scopolamine.

4. Process as specified in claim 1, consisting in the addition of a member of the group consisting of allyl and homologous esters of halogen hydracids.

5. Process for the production of quarternary salts of scopolamine, consisting in dissolving the scopolamine in suitable organic solvents for allyl and homologous esters, in reacting the solution with a member of the group consisting of allyl and homologous esters of strong acids and in reducing the compound formed with hydrogen in the presence of usual catalysts for hydrogenation.

6. As new substances the quarternary salts of scopolamine with a member of the group consisting of propyl esters of strong acids and butyl esters of strong acids.

7. As new substances the quarternary salts of scopolamine with the butylesters of strong acids.

8. As a new substance the scopolamine brombutylate with a melting point of 195–197° C.

9. As a new substance the scopolamine brompropylate with a melting point of 194° C.

GEORG SCHEUING.
WILHELM KRAUSS.

**Plaintiff's Ex. No. 25**

Jan. 13, 1957

## PREPARATION OF SCOPOLAMINE BROMBUTYLATE

Run I

Materials

| | |
|---|---|
| Scopolamine | 9.5g |
| $CH_3CN$ | 4.4cc |
| $CH_3CH_2CH_2CH_2Br$ | 2.55g |

Mixed in a ball joint Erlenmeyer, stoppered tightly and placed in wax bath at 65° — T variation ~ 2°.

Time in, 2:15 PM

Jan. 20, 1957

Flask removed at 10:15 AM. Solvent evap. on hot plate. Abt. 20cc $CH_3OH$ added and flask set aside.

Jan. 25, 1957

Product chilled (ice box), filtered and washed with cold methanol. Some loss noted on washing. Yield 4.80g 34% (Dried in Vac Oven at 80°) $AgNO_3$ and dil. $HNO_3$ added to filtrate. Wt AgBr 1.46g.

Run II

Feb. 20, 1957

| | |
|---|---|
| Scopolamine | 5g |
| Abs $C_2H_5OH$ | 20g |
| $CH_3CH_2CH_2CH_2Br$ | 4.33g |

Mixed in stoppered Erlenmeyer and stored at room Temp.

Run III

| | |
|---|---|
| Scopolamine | 5g |
| $CH_3CN$ | 3.46cc |
| $CH_3CH_2CH_2CH_2Br$ | 9.61g |

Handled as in II.

March 2, 1957

Run IV

In 4 PM

| | |
|---|---|
| Scopolamine | 5g |
| Acetone | 2.31g |
| $CH_3CH_2CH_2CH_2Bb$ | 2.94g |

Handled as in Run I

Run V

In 4 PM

| | |
|---|---|
| Scopolamine | 5g |
| Abs. Ethanol | 20.0cc |
| $C_4H_9Br$ | 4.33g (3.38cc) |

Handled as in Run I

March 3, 1951

Out at 10 AM
Solvent evaporated on hot plate (Runs IV and V)
~ 15cc methanol added to each—products set aside to crystallize. Out at 10 AM

April 2, 1957

Products of rns IV and V chilled, filtered, dried in Vac oven at 80°.
Run IV Wt. 2.94g, 40% Run V Wt. 1.64g, 21%

April 2

Product of Run 1. m.p. 136 to 139
Recrystallized from methanol and dried in Vac oven at 80°, to const wt. m.p. 142.5-144.
Samples from runs 1, IV and V made up in 3% solu. in 25cc Vol. flasks.

April 5

| | I | IV | V |
|---|---|---|---|
| $(\alpha)_{D}^{20}$ | 20.5 | 20 | 21 |

April 7

Runs II and III worked up in standard fashion.

April 8

Products collected as usual.
Wt Run II 0 Wt Run III 2.89g (39%)
Br in filtrates precipitated as $AgNO_3 . H_2O$
Wt Run III 0.71g Wt Run II 0.26g

April 9

Run VI

Scheuing Procedure

| | |
|---|---|
| Scopolamine | 5g |
| Ethanol | 25cc |
| Crotonyl Bromide | 5cc |

In 3 PM

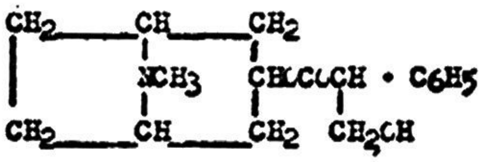
April 10

Out 3 PM
Product filtered, washed and dried in Vac oven at 40°.
Yield 3.5g

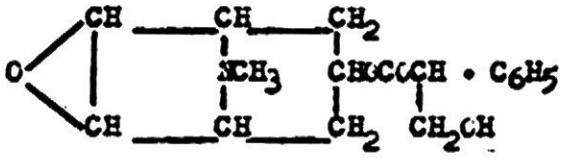
This was mixed with ∼ 10cc methanol. .5g 1% Pd on activated C added and $H_2$ added at 30° till absorption very slow. Cat. filtered, solvent evaporated on hot plate, ether added, messy crystals formed slowly from oil. Check Check crystallization on known Scopolamine HBr. — same behavior. $CH_3CN$ better. Recrystallize product from $CH_3CN$ (ether precipitation). Dry in Vac oven at 100°.

| | known Scopolamine HBr | Run VI | Mixed |
|---|---|---|---|
| MP | 195.5-197<br>darkens | 193-195<br>darkens | 194-195.5<br>darkens |
| Mixed MP with Scopolamine Bromobutylate | 115-126 | 116-126 | |

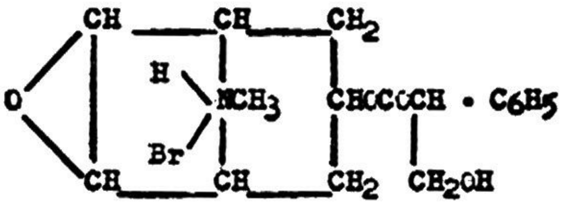
**Plaintiff's Exhibit No. 28**



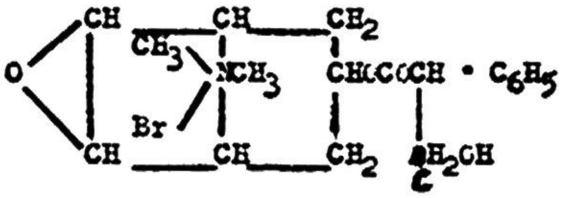
**Atropine**



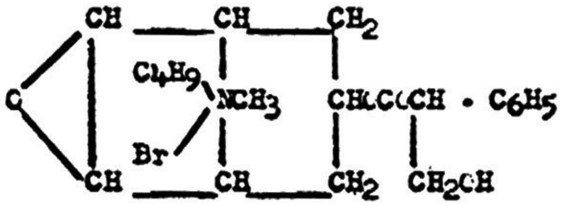
**Scopolamine.**



**Scopolamine Hydrobromide**



**Scopolamine Bromomethylate**



**Scopolamine Bromobutylate**

$CH_3CH = CHCH_2Br$

**Crotonyl Bromide**

0

P 14

**BRIEF FOR APPELLEE**

IN THE

# United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA

No. 14,181

C. H. BOEHRINGER SOHN, A PARTNERSHIP,
APPELLANT

*v.*

ROBERT C. WATSON, COMMISSIONER OF PATENTS,
APPELLEE

United States Court of Appeals
For the
District of Columbia Circuit
FILED DEC 19 1957
Joseph W. Stewart
CLERK

Appeal from the United States District Court
for the District of Columbia

## BRIEF FOR THE COMMISSIONER OF PATENTS

CLARENCE W. MOORE,
*Solicitor, United States Patent Office.*

J. SCHIMMEL,
*Of Counsel.*

## STATEMENT OF QUESTIONS PRESENTED

In the opinion of appellee the questions presented are:

1. Whether the trial Court's ruling that applicant's product does not come within the rule permitting the patenting of homologues possessing new and unexpected properties is so clearly erroneous as to justify or warrant reversal thereof, where the prior patent not only describes adjacent homologues of the claimed compound, but also describes a procedure which will produce the claimed compound and suggests to one skilled in the art that the claimed compound might possess the beneficial properties asserted therefor?

2. Whether, where the compound defined in the claim at issue is described by the identical name in a prior United States patent, anticipation under Section 102(a) of Title 35 U.S.C., providing that for a thing to be patentable it must not "have been described in a patent or a printed publication, is avoided merely because the process described therein for its production may be inoperative?

3. Whether, where the prior patent relied upon as anticipatory is appellant's own United States Patent having a claim for the identical compound defined in the claim at issue, appellant is estopped to assert that the process disclosed therein is inoperative to produce the claimed compound?

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IN THE

# United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA

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No. 14,181

C. H. BOEHRINGER SOHN, A PARTNERSHIP,
APPELLANT

*v.*

ROBERT C. WATSON, COMMISSIONER OF PATENTS,
APPELLEE

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**Appeal from the United States District Court
for the District of Columbia**

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## BRIEF FOR THE COMMISSIONER OF PATENTS

### Introduction

This is an appeal (J. A.-59) from the judgment (J.A.-57) of the United States District Court for the District of Columbia, entered May 6, 1957, dismissing appellant's complaint (J.A.-1) against the appellee, Commissioner of Patents, in an action brought under the provisions of Section 145 of Title 35 United States Code, in which appellant sought a decree authorizing appellee to grant letters patent of the United States to appellant (Plaintiff) based upon and containing certain claims (numbered 5 through 10 inclusive, 12 and 13) of a patent application Serial

No. 251,840, filed on October 17, 1951 by Franz Adickes, entitled "Scopolamine-Bromobutylate and Process of Producing Same"; and from an order denying a Motion for Modification of Judgment and for New Findings of Fact entered on June 10, 1957. Appellant is the assignee of the entire right, title and interest in and to said application, the assignment having been recorded in the United States Patent Office (J.A.-1).

The complaint was dismissed by the trial court after a hearing at which appellant introduced expert testimony and numerous documentary exhibits in the effort to prove patentable invention in the claimed subject matter. After taking the matter under advisement the Court rendered an opinion (J.A.-52) sustaining appellee's (defendant's) refusal to grant letters patent, concluding that "neither the product nor process claims are patentable over the prior art." Findings of Fact (J.A.-53), Conclusions of Law (J.A.-56) and judgment (J.A.-57) dismissing the complaint were entered. Notice of appeal was filed on August 6, 1957, after the Court denied a Motion for Modification of Judgment and for New Findings of Fact, the motion being restricted to a single claim, product claim 10 (J.A.-57). While the notice of appeal does not so indicate, appellant's brief clearly states that this appeal is "only as to claim 10" (Br-2), the other claims denied by the District Court directed to the Method of making the product of claim 10, not being involved in the appeal.

## APPELLANT'S APPLICATION

The specification of the patent application involved in this appeal is reproduced in the joint appendix (J.A.-61). As there indicated the alleged invention is concerned with the production of scopolamine-bromobutylate which possesses therapeutic properties. The production of that compound is said to take place by the action of excess n-butyl bromide on scopolamine base, dissolved in an organic solvent of strong polar character, including alcohol, the scopolamine-bromobutylate crystallizing out slowly, at temperatures of 65° C., in about a week or more (J.A.-61). The product is said to have a melting point of 142-144° C. and to be pure (J.A.-62).

## THE CLAIM

The subject matter of the claim for which appellant seeks to obtain a patent is set forth in claim 10 as a new product, defined both by its chemical name—scopolamine-bromobutylate and its structural formula. It appears in the appendix in the decision of the Board of Appeals (J.A.-82) and in appellant's brief (Br-3). In addition to the chemical name and structural formula the claim states that the product has a melting point of about 142° to 144° C.

## THE PRIOR ART

The District Court's decision is based solely on the fact that the prior art, as evidenced by the German patent to Merck, No. 145,996, issued on November 2, 1903 (J.A.-102) negatived patentability in the product defined in claim 10. However, the Board of Appeals of the Patent Office had also considered the U.S. patent Scheuing et al., No. 2,305,460, issued December 15, 1942 (J.A.-107), as part of the prior art, and had affirmed the examiner's rejection of that claim on the Scheuing et al. patent (J.A.-88). Before the trial Court appellee had also urged anticipation of the Scheuing et al. disclosure, but that Court did not decide that issue. Inasmuch as the Scheuing et al. patent is considered to be a valid part of the prior art, it will be treated and applied herein.

The Merck German patent of 1903 describes a process of producing the bromo methylates and the bromo ethylates of alkaloids of the tropeine and scopoleine group by reacting methyl or ethyl bromide at ordinary temperature with the free alkaloids or their solutions in ethanol, acetone, chloroform or the like solvents (J.A.-105). Example 5 is specific to the production of scopolamine-bromomethylate (J.A.-104). These compounds are said to be distinguished over the original alkaloids in that they are entirely free of undesired side-effects or at least such effects are greatly reduced.

The Scheuing et al. patent describes new quarternary salts of scopolamine and a process of producing the same, and specifically names scopolamine brombutylate as such a new compound in claim 8 (J.A.-108).

## SUMMARY OF ARGUMENT

1. The compound defined by claim 10 at issue here is a homologue of compounds old in the prior art represented by German patent No. 145,996.

Homologues are members of a series of compounds whose structure differs regularly by some radical from that of its adjacent neighbors in the series. Homologues are understood to have the same principal properties, but it is recognized and well known that the properties vary from member to member, and that knowledge of the properties of one of the members suggests to the skilled person the properties of other members. Also, homologues can usually be prepared by similar procedures or variations in known procedures obvious to the skilled chemist.

The statute (35 U.S.C. 101) authorizes the grant of a patent only where novelty, utility, and invention coexist and there is an advance over the prior art. The established rule with respect to homologues is that a new homologue is not such an advance over an adjacent member of the series as requires invention, unless the beneficial properties realized in the new compound is clearly outside of the expectations which knowledge of his science would inform the trained chemist should be inherent in the product. In the instant case, the specification of the application at bar indicates that the beneficial property of the new compound is in the field of therapeutics, and the evidence produced to show utility indicated a great degree of freedom from undesirable side effects (advantages which were undisclosed in the application). The German patent, however, had indicated that the prior art homologous compounds were distinguished over the original alkaloid base by strongly reduced undesired side effects, and therefore it would appear that this asserted unexpected beneficial property was not clearly without the expectation of one skilled in the art, particularly in view of the statements in the German patent. The record is clear that the finding of the trial Court that appellant's product does not come within the rule permitting patenting of homologues is not clearly erroneous; it should be affirmed.

2. The patent to Scheuing et al. issued in 1942 describes and claims the identical compound defined in claim 10 at issue. The law [35 U.S.C. 102(a)] is clear that if a thing for which patent is sought is described in a prior patent or publication the later applicant is barred. The decisional law interpretating the statutory provision is consistent in holding that the operability or inoperability of the process described in the prior patent is of no legal consequence on this question. Hence, appellant's showing that the described process will not produce the described compound is ineffective to remove this patent as an anticipation. Moreover, appellant should be estopped to assert inoperability of the patent and hence invalidity thereof in this proceeding. To permit a party to impeach his own patent, which is presumptively operative and valid, in order to obtain a new patent for the same thing has no basis in the law. Under the circumstances of this case the patent to Scheuing et al. is a complete anticipation of the claim at issue.

## THE ARGUMENT

### 1. Unpatentability Over The Merck Patent.

Appellant seeks to patent by virtue of claim 10, a chemical compound, quarternary scopolamine-bromobutylate, also called butyl scopolamine bromide (Br.-8). There is no question and no dispute about the fact that the German patent to Merck (J.A.-102) describes expressly closely related compounds, namely methyl and ethyl scopolamine bromide. Appellant concedes that this patent discloses those compounds (Br.-4). Further, there is no question but what those prior compounds are homologues of the compound defined in claim 10. Appellant clearly and specifically admits that fact (Br-9). Hence, the essential question at issue as to this prior teaching is whether the homologous compound defined in claim 10—scopolamine-bromobutylate—is patentable over those prior art compounds, i.e., scopolamine bromomethylate and scopolamine-bromoethylate.

Webster's International Dictionary (2nd Ed.) defines homology as:

> "the relation existing between the compounds of a series whose successive members possess, in addition to similarity of structure, a regular difference in formula. It is usually attended by a regular variation in physical properties. The term is used especially with reference to series of carbon compounds in which the regular difference is $CH_2$ * * *."

Hackh's Chemical Dictionary (3rd Ed.) defines homology as:

> "the similarity of organic compounds and their gradation of properties, as shown by the homologous series obtained when they are arranged in order of the number of carbon atoms they contain";

and defines a homologue as:

> "a member of a series of compounds whose structure differs regularly by some radical (e.g. —$CH_2$) from that of its adjacent neighbors in the series."

The question of the patentability of a compound over an old homologous compound has been considered many times by the Court of Customs and Patent Appeals. That Court has established a rule in such cases which it has uniformly and consistently followed. In effect, that rule is that "the nature of homologues and the close relationship the physical and chemical properties of one member of a series bears to adjacent members is such that a presumption of unpatentability arises against a claim directed to a composition of matter, the adjacent homologue of which is old in the art." *In re Henze*, 37 CCPA 1009, 181 F. (2d) 196. In such cases the burden is upon the applicant to rebut the presumption of non-patentability.

The statute (35 U.S.C. 101) permits or authorizes the grant of a patent only where novelty, utility and invention coexist, and there is an advance over the art. *In re Henze, supra.* In the instant case, appellee raised no issue as to the presence of novelty, insofar as the Merck patent is concerned, or even as to utility inasmuch as the specification of the application at bar stated that the claimed compound possessed therapeutic properties. The real issue here is one of invention or want of invention. As pointed out in the *Henze* case, *supra*, "to those skilled in the chemical art, one homologue is not such an 'advance' over an adjacent member of the series as requires invention, unless the beneficial properties realized in the new compound lie clearly outside of the expectations which knowledge of his science would inform the trained chemist should be inherent in the product." Also as indicated by this Court in *Dow Chemical Co.* v. *Coe*, 76 App. D. C. 317, 132 F. 2d) 577, chemistry as a science is not so unpredictable as to mark the production of every new material as inventive and patentable. It is well understood by chemists that the members of a homologous series of chemical compounds possess the same principal characteristics, that generally the chemical and physical properties of the individual members vary gradually from member to member; and that knowledge of the properties and chemical behaviour of one of the members suggests to the chemist the properties and chemical behaviour of the other members. Ordinarily also they can be prepared by similar procedures. Therefore, given a process for producing the homologous compounds of the German patent, any chemist would normally and naturally infer that the homologue defined in claim 10 at issue here could be produced in the same way. The facts of record in this case show that to be true, for the method disclosed in appellant's application is essentially the same as that disclosed in the Merck patent, as held by the trial Court (Findings of Fact Nos. 7-10—J.A.-55), except for minor variations, admittedly obvious to any skilled chemist (Br-10). Since the compound claimed involves only what would naturally occur in the development of the art, the skill of the art being sufficient to its production, known procedures for producing homologous compounds being available, it would seem that the inventive faculty has not been exercised. That is the established rule in these situations—*In re Wietzel et al.*, 17 CCPA 1079, 39 F. (2d) 669, even where the results obtained are better than the expected. *In re Gauerke*, 24 CCPA 725, 86 F. (2d) 330. In other words, if it is obvious or within the skill of the art to produce the compound claimed because of the prior production of homologous compounds, one who first produces such compound, utilizing the known procedures, has exhibited only the skill of the calling, and not invention. Lacking the statutory prerequisite of invention, the claim is unallowable, and no authority exists for the grant of a patent therefor.

Appellant contends, however, that the presumption of non-patentability arising against the compound defined in claim 10 because of the presence in the prior art of homologous compounds does not apply here because the new homologue has new and unexpected advantages (Br-10). Further, appellant contends that the true invention in this case is the discovery of the unexpected properties of the new compound (Br-10), which properties, it is asserted, would not have been obvious to one skilled in the art (Br.-15). This contention of appellant would appear to be an assertion that patentability of a homologue is conclusively established if it can be shown to have new and unobvious properties (Br-7). However, it is significant that the Court of Customs and Patent Appeals rejected a similar contention in *In re Finley*, 36 CCPA 998, 174 F. (2d) 130, where the appellant construed the Court's rule as to homologues, set out in the cases of *In re Hass et al.*, 31 CCPA 895, 903, and 908, 141 F. (2d) 122, 127, and 130, as holding that if a new and useful product does show unobvious or unexpected beneficial properties it follows that such a product is patentable, the Court said:

> "We did not affirmatively or even by implication so state in our decisions there. Our statement meant merely that unless a product does show the defined characteristics it is not patentable. Even if they be shown, the consideration of other factors may be required."

Further, it should be noted that in *In re Loring Coes, Jr.*, 36 CCPA 1067, 173 F. (2d) 1012, that Court also held that a mere difference in degree is not the marked superiority which ordinarily will remove the presumption of unpatentability of adjacent homologues of old substances.

As previously pointed out the established rule as set out in the *Henze* case, *supra*, recognizes that if the beneficial properties realized in the new homologue lie clearly outside of the expectations which knowledge of his science would inform the trained chemist should be inherent in the product "it may be possible to say that inventive genius and not mere skill of the calling was required to select the new compound, otherwise not." The trial Court found "that applicant's product does not come within the rule permitting patent of homologues possessing new and unexpected properties" (J.A.-53). That finding was based upon the fact that the Merck patent (J.A.-102) discloses that bromides of derivatives of the scopoleine group are advantageous as compared with the original alkaloids, in that they are either entirely lacking in undesirable secondary effects, or at least these are greatly diminished, whereas the desired properties of the plant bases are retained in them. In other words, in view of the Merck teaching the alleged new and unexpected properties of the compound of claim 10 do not lie clearly outside the expectations which the skilled chemist or pharmacologist would believe to be inherent in such a compound. That finding of the trial Court may be set aside only if it is clearly erroneous. *Esso Standard Oil Co.* v. *Sun Oil Co.*, 97 U. S. App. D. C. 154, 229 F. (2d) 37, cert. denied 351 U. S. 973; *Standard Oil Development Co.* v. *Marzall*, 86 U. S. App. D. C. 210, 181 F. (2d) 280.

Appellant urges that the District Court erred in construing the Merck patent, to refer to bromides of alkyl derivates of scopolamine (Br-16) in Finding of Fact No. 6 (J.A.-55), contending that the patent is limited solely to the methyl and ethyl derivatives and that, therefore, this foreign patent can be used only for what is precisely disclosed therein, citing *Becket* v. *Coe*, 69 App. D. C. 53, 98 F. (2d) 332. Appellee submits that the use of the broad terminology "alkyl bromides" by the patentee is a clear disclosure to those skilled in the art that other bromides in addition to the methyl and ethyl bromides specifically named could be used also, and since a clear disclosure is all that is necessary to make the foreign reference applicable there was no error or misconstruction by the trial Court. Furthermore, the rule relating to the use of foreign patents as references was stated by the Court of Customs and Patent Appeals to be—*In re Sherman*, 26 CCPA 1337, 104 F. (2d) 619, as follows:

> "Upon the question of the weight to be given a foreign patent cited as a reference, whatever else may be said, it is well settled that it is not required that the patent describe the identical thing in order to be a reference, and where there is a difference the question of whether such difference involves invention or mere mechanical skill must be considered."

Under that rule the Court approved the combining of a foreign patent with others to show that the difference was not inventive—*In re Cross*, 20 CCPA 710, 62 F. (2d) 182 and *In re Sherman*, *supra*—a practice which this Court also approved in *Davies* v. *Coe*, 65 App. D. C. 345, 83 F. (2d) 602.

Applying the above rule to the facts of the instant case, it is to be noted that one of the differences from the patent disclosure is the use of the butyl bromide as the "alkyl bromide." Finding of Fact No. 8 (J.A.-55) states that the differences between the appellant's process and the prior art process (i.e., the Merck patent) are such that the subject matter as a whole would have been obvious to a person of ordinary skill in the art. That finding is conclusive against appellant in this appeal. That being true it is submitted that the reference is a valid reference for everything it reasonably teaches one skilled in the art. Hence, there is no error in Finding of Fact No. 6.

Appellant also asserts that Merck's statements as to the secondary or side-effects are inaccurate, basing this assertion on evidence which is said to show that Pamine, the scopolamine bromomethylate of the Merck patent (J.A.-36) actually had worse side effects than scopolamine hydrobromide or atropine (Br-17). Apart from the fact that the patent is comparing the bromide of the alkyl derivative of scopolamine with the original alkaloid (J.A.-102) and not the hydrobromide thereof, and hence it is questionable whether such evidence is adequate or sufficient under the rule of *Blanchard* v. *Ooms*, 80 U. S. App. D. C. 400, 153 F. (2d) 651, it should be noted that the new and unobvious properties relied upon by appellant to show invention (Br-15) appear to have been discovered subsequent to the filing of the application at bar, since there is no disclosure in the application of these properties. All that the application states is that the compound "possesses remarkable therapeutic properties" (J.A.-61). Ordinarily, advantages or unexpected results of which the applicant knew nothing when he filed the application, as must be inferred since they are not mentioned in the application, cannot be relied upon to show invention. *Abbott* v. *Coe*, 71 App. D. C. 195, 109 F. (2d) 449. Furthermore, the mere fact that the claimed

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compound is more effective than the prior art compound, or that it may be used in smaller amount to obtain the same or even better results leading the trial Court to find that it (the claimed compound) has great utility because of an unexpected degree of freedom from undesirable side effects (Finding of Fact No. 11—J.A.-56) constitutes no more than a difference in degree. Chemists know that while homologous compounds possess the same principle characteristics or properties they know also and expect a variation in properties, chemical, physical, and pharmacological, between homologues. The definition of homology, given above, includes variations in properties. Under these circumstances, it is submitted that even though the difference in properties is characterized by the trial Court as unexpected, the difference is but one of degree, and that such a difference is not an inventive or patentable one. *In re Crosley et al.*, 34 CCPA 882, 159 F. (2d) 735. Also, while it is true as appellant contends that there is no true teaching in the art of the advantages of the claimed compound, that fact is of no legal consequence in this case. The claim sought here is for the compound *per se*, not for any particular therapeutic application or use thereof. In determining the question of patentability the Court does not view the prior art from the eyes of a novice or layman, but rather as one skilled in the art to which the subject matter relates. *Sinclair & Carroll Co.* v. *Interchemical Corp.*, 325 U. S. 327; *Radtke Patents Corp.* v. *Coe*, 74 App. D. C. 183, 122 F. (2d) 937. Since the skilled person knew that the process for making homologues of the claimed compound was applicable to that compound, and since it was suggested in that prior art that the homologues possessed favorable properties as compared with the original alkaloid, the mere fact that experimentation with the compound when produced results in the discovery of properties surpassing or even not possessed by the prior art compounds, which may seem remarkable to the public generally, is not, under the law, sufficient to convert what was obvious and within the skill of the art into invention. *Radtke Patents Corp.* v. *Coe, supra.*

Accordingly, it is submitted that the finding of the trial court that the product defined in claim 10 is unpatentable in view of Merck German patent No. 145,996 is not clearly erroneous and that the decision should be affirmed.

2. Anticipation by Scheuing et al.

The answer to appellant's (plaintiff's) complaint (J.A.-4) includes as a defense the references and reasons relied upon in the examiner's statement and in the decision of the Board of Appeals. Each of those tribunals rejected claim 10 as unpatentable over the disclosure in the Scheuing et al. patent (J.A.-107), which discloses and claims the same compound. The decision of the Board of Appeals discussed this ground of refusal in detail (J.A.-87, 88). Appellee urged this ground before the District Court, but that Court "assuming (without deciding) that there was no anticipation by the mere naming of scopolamine bromobutylate in the Scheuing patent" (J.A.-53) decided on other grounds. Further, appellee also urged before the trial Court that appellant was estopped to assert error in the naming of that specific compound by its own prior patent to Scheuing et al., and again the trial Court's opinion stated that the product claim was unpatentable on other grounds, "assuming further (without deciding) that the applicant is not estopped to impeach its own prior patent." Since appellee may urge any matter appearing in the record in support of the judgment appealed from, without a cross appeal—*U. S.* v. *Amer. Railway Express*, 265 U. S. 425—this Court is asked to consider this ground of defense, in the event that there is a reversal of the finding of the District Court that claim 10 is unpatentable over Merck German patent No. 145,996.

That the patent to Scheuing et al, names scopolamine bromobutylate as the compound produced by the procedure set forth in Example 1 (J.A.-107); and that that compound is specifically claimed in claim 8 of the patent (J.A.-108) is apparent from a reading of those portions of the patent specification. Appellant's challenge to this ground of rejection was based upon a showing that it was discovered subsequent to the patent grant that the patentees were in error in their statement that the described procedure produced scopolamine-bromobutylate. This appears from the decision of the Board of Appeals, wherein, in answer to that challenge, it was pointed out that it is legally immaterial whether the procedure described does or does not produce the claimed compound (J.A.-87), supporting that holding by the citation of numerous decisions of the Court of Customs and Patent Appeals, and a decision of this Court (J.A.-88). In further exposition of that position of the Board of Appeals appellee points out that the applicable statutory basis for the rejection is Section 102(a) of Title 35 U.S.C., which section states that for a thing to be patentable to an alleged inventor it must not "have been described in a printed publication in this or a foreign country before the invention thereof by the applicant for patent." Appellee contends that the subject matter of claim 10 at issue here is described in the Scheuing et al. patent. The claim at issue calls for "quaternary scopolamine-bromobutylate." Claim 8 of Scheuing et al. defines "scopolamine brombutylate" and the description expressly states that the invention relates to "new quarternary salts of scopolamine." Appellant's claim also contains a structural formula designation, but the evidence is clear that the name is a word picture of the structure, as appellant's witness Dr. Sager testified (J.A.-50). Therefore, either name or structural formula is sufficient to constitute a description to one skilled in the art, and since the patent and the claim use identical language (there being no significance in the fact that an "o" is omitted by the patentee between "brom" and "butylate") to describe the compound, it is submitted that the patent contains a sufficient description under the law to negative patentability of the claim at issue.

The decisional law interpreting prior Sections 4886 and 4920 of the Revised Statutes is clear that if the thing claimed is described in a prior patent it is not necessary that there be an operative process for its production. Section 102(a) of Title 35 U.S.C. did not change the prior law. *New Wrinkle et al.* v. *Watson,* 92 U. S. App. D. C. 137, note 6; 206 F. (2d) 421. The landmark case on this question is *Cohn* v. *United States Corset Co.,* 93 U. S. 366, where the Supreme Court said:

> "It is quite immaterial, even if it be a fact, that the * * * is insufficient to teach a manufacturer how to make the patented corset. It is enough if it sufficiently describes the corset itself. * * * *the important inquiry, therefore is whether the prior publication described the article.* To defeat a party suing for infringement, it is sufficient to plead and prove that the thing patented to him had been patented or described in some printed publication prior to his supposed invention or discovery thereof. Revised Statutes section 4920. *What is required is a description of the thing patented, not of the steps necessarily antecedent to its production.*" (Italics added.)

This Court interpreted and applied the rule of the *Cohn v. Corset Co.* case in *In re Schaeffer,* 2 App. D. C. 1; *In re Decker,* 36 App. D. C. 104; *Eastman Kodak Co.* v. *Coe,* 78 U. S. App. D. C. 403, 135 F. (2d) 836; and *Merck & Co., Inc. et al.* v. *Marzall,* 91 U. S. App. D. C. 50, 197 F. (2d) 206. In the *Decker* case the patent relied upon to negative patentability was attacked on the ground that the disclosed devices were inoperative (just as here the patent is challenged because the process is said to be inoperative); but this Court was not impressed, holding that "since both * * * patents disclose a very complete *conception* of a paper barrel of the description and quality of the one on which appellant is here claiming a patent" (Italics added), it was deemed immaterial that the machines disclosed in the patents were inoperative to produce that product. Also, in the *Merck & Co.* case this Court, applying the same rule, said that where the application for a patent is on the compound itself "such an application must be denied if there has been any prior disclosure of the compound, even though no practical means for its isolation or manufacture was previously known."

In addition to those cases of the Court of Customs and Patent Appeals cited in the decision of the Board of Appeals (J.A.-88), appellee desires to call the Court's attention to two very recent cases on this phase of the law, namely, *In re Inman*, 43 CCPA 709, 228 F. (2d) 229 and *In re Baranauckas* et al., 43 CCPA 727, 228 F. (2d) 412. The latter in particular is significant because of the fact that that Court reexamined the whole question, and after making the comment that the reference (Straus) does not state that any of the compounds whose formulae he gives can actually be obtained by his process; that an affidavit of record indicated that they cannot; and that the settled rule of the *Von Bramer* and *Crosley* cases (J.A.-88) is that operability of a process is immaterial to the question of whether a prior description of a chemical compound is anticipatory, concluded that:

> "While it is true that Straus neither names nor gives the formula of the compound of appealed claim 22, it is our opinion that he discloses that compound in a sufficiently clear and definite manner to anticipate that claim. * * *

> Our position in the present case is dictated by what we conceive to be the necessary interpretation of the prior cases. We cannot see a logical distinction between this case, where the compound was revealed as clearly as if it had been explicitly named, and those cases in which it happened to be named explicitly. In this case it would not have changed the force or meaning of the reference in the slightest if it had specifically named each of the corresponding chlorine compounds. We can see no reason why we should hold an explicit naming of a compound to be an anticipation, and hold an equally clear, though implicit, disclosure not to be an anticipation.
>
> "At the same time, though our decision is compelled by the existing law, we feel constrained to point out that there are limits to the doctrine of those cases."

Clearly the decisional law of the courts whose decisions governs proceedings in the Patent Office show definitely that appellant's contentions are without merit. Further, it might be pointed out that other courts have also interpreted the statutory language in the same way and arrived at the same conclusion. See *One-Piece Bifocal Lens Co.* v. *Bisight Co. et al.*, 246 Fed. 450, affirmed 259 Fed. 275, cert. denied 249 U. S. 606; and *Gen. Elec.* v. *Deforest,* 17 F. (2d) 90. Accordingly, it is submitted that the overwhelming weight of authority supports appellee's position and that the patent to Scheuing et al. relied upon by the Patent Office tribunals as anticipatory negates patentability in the subject matter of claim 10.

Appellee contends also that appellant should be estopped to assert that the process described in the Scheuing et al. patent is inoperative and that the disclosure of scopolamine-bromobutylate therein is a nullity. Appellant admittedly was the owner of the application which matured into the patent, and as such had a potential monopoly on scopolamine brombutylate, by virtue of claim 8 of the patent (J.A.-108). That patent exists today as a presumptively valid patent (35 U.S.C. sec. 282). It is also presumptively operative. Its validity cannot be challenged in a proceeding under Sec. 145 of Title 35 U.S.C.; and yet that is exactly what appellant is trying to do by asking the Court to grant another patent to the same compound. Impeachment of the patent would seem to be absolutely necessary in order to grant the same claim to appellant in this proceeding. It would appear to be not only unreasonable and inequitable to permit appellant to start a new monopoly on a product which expires in two years by asserting that the patent is invalid, but also without sanction of law. Under analogous circumstances the Court of Appeals for the Eighth Circuit held estoppel to apply —*Rice-Stix Dry Goods* v. *J. D. Scriven Co.*, 165 Fed. 639—and it is submitted that this Court should apply the same doctrine in the event that it is necessary to reach this question.

## CONCLUSION

It is respectfully submitted that the claim sought is unpatentable under the law; that the conclusion reached by the Patent Office tribunals and the District Court that the chemical compound defined by the claim at issue is unpatentable over the disclosure of homologous compounds in the German patent to Merck No. 145,996 was correct and has a rational and reasonable basis in the record; and that the conclusion reached by the Patent Office tribunals as to anticipation by the Scheuing et al. patent No. 2,305,460 was correct. Further, it is submitted that under the circumstances of this case appellant is not entitled to obtain the claim at issue since the same identical compound is claimed in its own prior patent and appellant should be estopped to impeach the validity of that patent. The decision appealed from should be affirmed.

Respectfully submitted,

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J. SCHIMMEL,
*Of Counsel.*

December, 1956

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## REPLY BRIEF FOR APPELLANT

IN THE

# United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

United States Court of Appeals
For the
District of Columbia Circuit
FILED JAN 8 1958
Joseph W. Stewart
CLERK

## Appeal No. 14,181

C. H. BOEHRINGER SOHN, a Partnership, *Appellant*,

v.

ROBERT C. WATSON, Commissioner of Patents, *Appellee*.

**Appeal from the United States District Court for the District of Columbia**

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PRESS OF BYRON S. ADAMS, WASHINGTON, D. C.

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**Appeal from the United States District Court for the District of Columbia**

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## REPLY BRIEF FOR APPELLANT

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### INTRODUCTION

In addition to the reply to appellant's brief, the brief for appellee raises certain additional defenses, not passed on by the District Court. It is therefore necessary first to answer appellee's argument in support of the judgment below, and then to cover the other issues.

## STATEMENT OF FACTS

In the portion of its brief entitled "The Prior Art", appellee (page 4) omits certain very important facts in discussing the Scheuing patent. First, the brief fails to state that the product produced in the manner described in Scheuing is *not* scopolamine brombutylate; and, second, it omits the fact that the pharmaceutical properties and melting point of the compound described in Scheuing are *not* those of scopolamine brombutylate.

## APPELLEE'S SUMMARY

In point 1, appellee says that the "asserted beneficial property (of Buscopan) was not clearly without the expectation of one skilled in the art". But the District Court found the properties of Buscopan to be unexpected. And the evidence shows that, whereas the compounds of Merck (brommethylate and bromethylate) are *in fact* not substantially different from scopolamine in undesirable side effects, the compound of claim 10 is *really* free of such undesirable properties.

In point 2, again, appellee ignores the misdescription and misnaming of the product in Scheuing.

## ARGUMENT

In connection with Merck, appellant fully agrees with appellee that there is a presumption of unpatentability of one homolog over another. But it urges that this presumption is overcome once *unexpected* properties are shown in the homolog. Particular reference is made here to the language of the statute, quoted and discussed beginning at the bottom of page 7 of our main brief.

In the cases relied on by appellee (pages 8, 11) (*In re Henze,* 37 CCPA 1009, 181 F. 2d 196; *In re Hass et al,* 31 CCPA 895, 903 and 908, 141 F. 2d 122, 127 and 130), there was in each instance a finding that the claimed compound had not been shown to have any unobvious properties as compared with its known homologs.

*Dow Chemical Co.* v. *Coe,* 76 App. DC 317, 132 F. 2d 577 (page 9) is totally irrelevant. If we could not show unobvious results, we would not contend that claim 10 is patentable.

*In re Weitzel* (page 10), 17 CCPA 1079, 39 F. 2d 669 (relating to process claims) states (page 672):

> "Where there is no real reason to *suppose* that the result would not be produced there is no invention in trying it and finding out that the process is successful". (Emphasis added)

All this may be true, but no chemist, knowing the properties of the compounds of Merck, would have any reason to suppose that Buscopan would have entirely different properties. The District Court's finding of unexpectedness belies any such argument.

*In re Gauerke* (page 10), 24 CCPA 725, 86 F. 2d 330, relates to the discovery of an additional function of a device invented by another, and is wholly irrelevant to the issue being discussed here.

*In re Finley* (page 11), 36 CCPA 998, 174 F. 2d 130, was decided on the basis that the tests made did not show any unexpected properties for the compound claimed. The quotation from this case on page 11 of appellee's brief is pure dicta—but even then it does not say that homologs of known compounds may not be patentable, and the statute, we submit, clearly makes them patentable if the differences over the prior art are unobvious.

*In re Coes, Jr.* (page 11), 36 CCPA 1067, 173 F. 2d 1012, involved a claim to a product which was actually worse than the prior art, the products of which were more efficient than the one claimed. But even if it were authority for the proposition that a mere difference in degree is not the marked superiority which ordinarily will render a homolog patentable, it is submitted that the differences between Buscopan and the Merck compounds are so great as to be more than a difference in degree, Buscopan being of the order of 70 to 1500 times less in side effects (our main brief, page 15). In other words, Buscopan is practically entirely free of undesirable properties which exist in the prior compounds to a very substantial degree.

As has been repeatedly pointed out, the compounds of Merck are not, *in fact,* free of undesirable side effects. This was known to those skilled in the art, as shown by Plaintiff's Exhibit 6 (Tr. 92) published in 1942 where the table on page 93 shows methyl-scopolamine bromide (the same as the scopolamine bromomethylate of Merck) to be substantially the same as scopolamine hydrobromide in inhibition of saliva. The mydriatic effect (dilatation of the eye) of the Merck compound was also found to be about the same as, and its effect on the pulse greater than, that of scopolamine hydrobromide. So it is apparent that the almost complete freedom of Buscopan from side effects *was* unexpected and unobvious.

On the question of the value of a foreign patent as a reference, appellee cites this Court's decision in *Davies* v. *Coe,* (page 13), 65 App. DC 345, 83 F. 2d 602. It is significant that the Court there held that the patent should be granted to appellant, and stated that a foreign patent is good only for "what is clearly and definitely expressed in it" (p. 603). As is shown in our main brief (page 16), the higher alkyl compounds are *not* "clearly and definitely" referred to in Merck.

The appellee's brief (page 14) infers that tests should have been made of the differences between scopolamine base and the Merck compounds. But "scopolamine", when used as a medical term, means scopolamine hydrobromide. This is clearly shown by the Merck Index, an authoritative index of chemicals, which states (6th Edition, 1952, page 853) that scopolamine is unstable, and that its use in medicine is in *the form of scopolamine hydrobromide.* So it is fair to assume that when the Merck patent speaks of the side effects of scopolamine, it means the side effects of the form of scopolamine commonly used by physicians, namely the hydrobromide. But, in any case, the differences between the methylate of Merck and Buscopan are clearly shown to be so great as to be outstanding and unexpected.

The allegation by appellee (page 14) that the new and unobvious properties appeared to have been discovered subsequent to the filing of the application is totally unwarranted and misleading. It ignores the paragraph (second paragraph, Tr. 62) which states:

> "Also, the information contained in the German patent, to the effect that scopolamine-bromobutylate is some ten times more strongly active than scopolamine in rabbits eyes is not correct. Actually the activity of scopolamine-bromobutylate is at least 200 times less effective than that of scopolamine and about 500 times less effective than that of atropine. By reason of this advantageous property as well as the fact that with scopolamine-bromobutylate the action on the heart amounts to only 1/30th that of atropine, whilst the action on the stomach, gut and gall bladder is about equal to that of atropine and the far-reaching non-toxicity, scopolamine-brombutylate has a very extraordinary importance as a spasmolytic."

Now here are actual figures as to two of the side effects referred to in the testimony, as well as a general statement of "far-reaching nontoxicity", combined with the statement that the spasmolytic action is about equal to that of atropine. How can appellee argue in good conscience that "there is no disclosure in the application of these properties"?

Furthermore, it has been held in the Patent Office that, where there is disclosure of utility, data obtained subsequent to the filing of the application may be used to show that a claimed compound possesses unobvious properties as compared to the compounds of the prior art. This was clearly stated by the Board of Appeals in *Ex parte Ladd et al.*, 112 USPQ 337, 338, where the Board said:

> "We are of the opinion that as long as the appellants have disclosed the compound and its utility they may establish by means of data obtained subsequent to the filing of the present application that it possesses unobvious properties as compared to the compounds of the prior art."

*In re Crosley et al* (page 15), 34 CCPA 882, 159 F. 2d 735, related to a claim to a compound in a more stable form, having no different therapeutic properties. Differences in degree did not enter the picture.

The remaining decisions cited on pages 15 and 16 of appellee's brief are of a general nature. We have shown that the art *knew* (plaintiff's Exhibit 6, Tr. 92) that the Merck compounds had substantial undesirable side effects. We have shown that the use of the term "alkyl" in Merck is in every case associated *only* with the methyl and ethyl compounds. The trial Court has found that Buscopan *has* unexpected properties. We submit that under the patent statute the facts do not justify the refusal of a patent to applicant upon the basis of what is disclosed in the German patent to Merck.

### Other Defenses

The brief for the appellee raises two further questions on which the Court below did not pass. These questions are:

1. Does the mere naming of a chemical compound, with a description of a process which does *not* produce the compound named and with the description of properties *not* actually possessed by the compound constitute an anticipation?
2. Was the filing by appellant of an application in the United States containing this misdescriptive matter and claiming a compound by the same name, but

giving the wrong melting point, enough to estop appellant here, merely because, by an act of the Government, a patent was caused to issue on such application, which patent was never owned by appellant?

### The Scheuing Patent

This patent, plaintiff's Exhibit 24 (Tr. 107), describes in Example 1 a procedure the product of which the patentee names" scopolamine brombutylate" (second column, lines 26-27). This product is said to have a melting point of 195-197°C. Likewise, the patent states (column 1, lines 20-22) that the n-butylscopolaminium salt (another name for scopolamine bromobutylate is ten times as strong as scopolamine when tested in a rabbit's eye. Finally, claim 8 of the patent covers scopolamine brombutylate *having a melting point of 195-197°C.*

The claim involved in this appeal covers a compound *having a melting point of 142-144°C.*

The evidence, which was uncontroverted, plainly shows that the procedure described in Scheuing *will not* produce scopolamine brombutylate, but actually gives scopolamine hydrobromide, an entirely different compound both in its nature and its effects. The evidence also proves that scopolamine brombutylate has a melting point of 142-144°C, and that it is much less effective in rabbits eyes than atropine—one five-hundredth, and not ten times as the Scheuing patent states.

Dr. Sager's testimony (Tr 44-46; 51; plaintiff's Exhibit 25, Tr. 111) is that he followed the procedure described in Example 1 of Scheuing and obtained a material (plaintiff's Exhibit 27) which he submitted to tests. He got a material melting at 195.5-197°C. Mixing this with a known sample of scopolamine hydrobromide, the same melting point was obtained. When however, he prepared scopolamine brombutylate in the manner described in the Adickes application (plaintiff's Exhibit 26) he found a melting point of 142.5-144°C. Finally, when he mixed the Scheuing and Adickes products, the melting point was 120°C, whereas, if they were the same product, a melting point of 195°C would be expected (Tr. 45).

Dr. Sager positively stated that "the materials have to be different" (Tr. 46), that they could not possibly be the same under any known chemical theories, that the Scheuing product (plaintiff's Exhibit 27) was "almost certainly scopolamine hydrobromide"; and that the mixed melting point test proved *beyond a doubt* that plaintiff's Exhibits 26 and 27 were *different* compounds.

Dr. Wick's evidence, fully discussed in our main brief and summarized in plaintiff's Exhibit 22 (Tr. 101), is to the effect that scopolamine brombutylate is only one five-hundredth as effective as atropine in producing pupil distention, while scopolamine hydrobromide is several times as strong (Tr. 19).

The fact then is that Scheuing made and tested scopolamine hydrobromide, melting at 194-196°C, and *not* scopolamine brombutylate. He then proceeded to *misname* his product. It is because of this misnaming that the Patent Office contends that a patent should be denied to appellant.

This, we submit, is making the question of patentability a matter of words, and not of scientific *fact*.

It is admitted that, given the name "scopolamine brombutylate", a skilled chemist could have written the formula appearing in claim 10 (Tr. 76). We will also admit, for purposes of this appeal, that a skilled chemist, knowing the Merck patent, could have produced scopolamine brombutylate. But, as the Court found (FF 11, Tr. 56), the art would not have expected the great utility and advantageous properties of this substance.

The issue then is whether the misnaming of a compound, giving it the name of a compound later produced by another inventor, the new compound having different chemical and physiological properties and being produced in a different way, should be enough to justify the denial of a patent to the *true* inventor. We submit that the answer to this question should be that it is *not*.

There have been some decisions which would appear to go so far as to say that the mere naming of a compound in the prior art is enough to constitute anticipation. However, the Court of Customs and Patent Appeals has, only recently, disclaimed any intention to follow such a rule. In the case of *Baranauckas,* 228 F. 2d 412, 416, that Court said:

> "Certainly they do not extend so far as to permit publication of theoretical lists of hundreds or thousands of possible compounds to deny patent protection on such compounds to those who actually discovered them later. The exact boundaries will have to be delineated on a case by case basis. But whatever they may be, we have not reached them here."

The authority of that decision was recognized by the Patent Office Board of Appeals, in ex parte *Herzog,* 115 U.S.P.Q. 195. That case involved a situation where, through error, there was a disclosure of what might have been an anticipation in a reference. The Board expressed an unwillingness to extend the doctrine of the earlier decisions, and granted the patent.

In its decision, the Board called special attention to the Baranauckas case. The language is as follows (page 197):

> "In the absence of more adequate information as to the compound actually contemplated by Gallagher we feel reluctant to extend the doctrine of *In re Crosley,* 34 CCPA 882, 1947 C.D. 216, 600 O.G. 172, 159 F. 2d 735, 72 USPQ 499, and *In re Von Bramer et al.,* 29 CCPA 1018, 1942 C.D. 463, 542 O.G. 183, 127 F. 2d 149, 53 USPQ 345, to apply to a representation which must be corrected in a particular manner to arrive at

> a significant compound which might defeat the appealed claims. Attention may be directed to the comments of the Court in the recent case of *In re Baranauckas et al.*, 703 O.G. 668, 108 USPQ 226."

Appellee relies heavily, on this phase of the case (page 19), on the decision of the Supreme Court in *Cohn* v. *United States Corset Co.*, 93 U.S. 366. That case is authority for the proposition that a description of an article in a prior publication anticipates, even though the method of producing it be not shown. But the question here is whether that rule is applicable to a completely erroneous description, which uses the wrong name to identify the product. The Cohn case refers to "a description of the thing patented". But the thing sought to be patented here, scopolamine brombutylate, melting at 142-144°C and practically free of mydriatic effect, is *not* the thing described in Scheuing, a compound having a melting point of 194-196°C and several times as active as atropine in mydriasis, even though the prior inventor *mistakenly* referred to this compound by the name of scopolamine brombutylate.

The qualifications on this rule are well expressed in the decision in *One-Piece Bifocal Lens Co.* v. *Bisight Co.*, 246 Fed. 413, relied on by appellee (page 21). There the Court said (page 416):

> "It is, however, certain that, before it can be held to do so [i.e. to anticipate], it must affirmatively appear, beyond the opportunity for reasonable question, that it does in all respects clearly, accurately and minutely portray the very thing claimed in the patent assailed."

Surely Scheuing does not "accurately and minutely portray" the compound sought to be patented here.

We have discussed above the *Baranauckas* case, cited at page 20 of appellee's brief. The companion *Inman* decision involved a situation of complete anticipation, and is irrelevant.

### The Rule Contended for by Appellee Is Unwarranted

The contention that the mere words "scopolamine brombutylate" in Scheuing should be taken out of their context and alone form the basis for a refusal of claim 10 is wholly unwarranted.

It is a well-settled rule of patent law that that which infringes, if later, anticipates, if earlier. This was expressed by the Supreme Court in *Miller* v. *Eagle,* 151 U.S. 185, where the Court said (page 203):

> "It admits of little or no question that if this Brown patent was one of later date than the Wright patent of 1881, it would be held to be an infringement thereof, and, under the authorities, 'that which infringes if later, anticipates if earlier.'"

Obviously any compound *identified* like that of Scheuing, having a melting point of 196°C, would *not* be the same compound as scopolamine bromobutylate having a melting point of 143°C, and would not infringe the product claim presented by plaintiff here. The Patent Office, we submit, should allow the rule of *Miller* v. *Eagle* to cut both ways, and should hold that that which does not infringe, if later, does not anticipate, if earlier, where the new compound has very beneficial and unobvious properties.

The proposition that the mere naming of a substance by some chemical name will anticipate an application disclosing and claiming that substance, and further disclosing an unobvious and unexpected utility of the product, would make of the patent law a mere matter of words and formalities, and not a matter of substance. There are literally millions of possible organic compounds and any one could sit down and write the names and formulae of hundreds of thousands of these without contributing anything to the art, since he would neither teach how these compounds could be produced or what their value to the art would be. It is utterly illogical that the inventor who actually produces a new compound and who discloses to the art its utility and value for a specified purpose should be debarred from a patent because there has been published in print the bare chemical name of that compound.

Yet this was the position taken by the Patent Office. It relied primarily on three decisions of the Court of Customs and Patent Appeals and on one decision of the Court of Appeals for the District of Columbia. The District of Columbia case is *Merck* v. *Marzall,* reported at 91 U.S. App. D.C. 50, 197 F. 2d 206. While that decision contains some language stating that "an application must be denied if there has been any prior disclosure of the compound, even though no particular means for its isolation or manufacture was previously known", the gist of the decision lay in the fact that one of the compounds included in the claims was a homolog of a compound described in the prior art. As we have explained above, a rejection of a claim to a homolog of a known compound is justified if the applicant shows no unexpected difference in effect between the new and the old. There was apparently no showing in the *Merck* case that thiamine mononitrate had any particular properties which distinguished it from the known monobromide, and the decision in that case is not applicable here.

This Court in the *Merck* case referred to its earlier decision in *Eastman Kodak* v. *Coe,* 78 U.S. App. D.C. 403, 135 F. 2d 836. That case, however, was no authority for the proposition broadly stated by the Patent Office, since it held that the compounds themselves, *and their usefulness for the purposes claimed,* had been disclosed by the references. In the present situation, the compound has not been disclosed except insofar as another compound was mistakenly given a name which is the same as that of the claimed compound (although with an entirely different melting point), nor does the prior art disclose the definite advantages of the claimed compound.

The Patent Office also relied on the decisions of the Court of Customs and Patent Appeals *In re von Bramer,* 127 F. 2d 149; *In re Crosley,* 159 F. 2d 735; *In re Kebrich,* 201 F. 2d 951.

The *von Bramer* case involved a situation in which a compound was not only named by its chemical name but was shown to have the same utility in the composition as was claimed by von Bramer. The claim was not directed to the compound per se, but to the use of this compound as an ingredient of a motor fuel. Furthermore, the Court held that the differences between the five-carbon atom compound of the application and the four-carbon atom compound of the reference were matters of degree only. In other words, the utility of the alleged new compound was clearly disclosed in the reference, and there was no patentable difference over other known compounds.

In the *Crosley* case, there was no denial by the appellant that the compound claimed was disclosed by the prior art, but only that his particular form of the compound, which was partially dried, was patentable over the previously known forms of the compound. The court held that this material differed only in degree from the prior art. Furthermore, the therapeutic effect of the compound was already known and the only difference was an improvement in the method of administration which the court held not to be a difference in kind.

*Kebrich,* while restating the rules of the earlier decisions to a certain degree, involved a situation in which the compound itself was known as a compoent of a mixture but perhaps not in purified form. The court found no limitation in the claim which would exclude the mixture, and therefore sustained the Patent Office's refusal of the claim. In the present case, as has been pointed out above, the product claim of this case could not but exclude the compound of Scheuing since the melting points are so totally different.

On the other hand, the District Court has recognized that the mere naming of a compound, if inaccurate, does not constitute anticipation (Judge Morris, in *Foremost Dairies* v. *Watson,* 107 USPQ 83). There certain language described a product allegedly produced by a certain process, this language having been held by the Patent Office to disclose the subject matter of the claim in issue. The evidence showed that such a product was not known, and that it did not have the desirable properties of the subject matter of the application. Judge Morris said (page 85):

> "Much of the hearing and of the briefs is concerned with the proposition as to whether an erroneous statement of the prior art is a disclosure which will prevent a patent of a subsequently discovered product. I think the decision in the case of *Mathieson Alkali Works* v. *Coe*, 69 App. DC 210, 99 F. 2d 443, 39 USPQ 96, decided December 26, 1938, is controlling. There it was held that a statement so contradictory to fact, as this was demonstrated to be, is not a part of the prior art. Here it has been amply established that the product erroneously referred to by Chuck was not a part of the prior art. In this view, I conclude that the plaintiff is entitled to the relief prayed for, and judgment will be entered accordingly."

It has been clearly demonstrated here (and, in fact, the Board of Appeals did not deny) that the product of Scheuing is "erroneously referred to" and that Scheuing's disclosure is "a statement . . . contradictory to fact".

The courts of other jurisdictions have likewise recognized that such disclosure did not constitute anticipation. Judge Learned Hand in *Dewey & Almy Chemical Co.* v. *Mimex Co.,* 124 F. 2d 986, clearly stated the test of anticipation as requiring a proper disclosure in the following language (page 589):

> "No doctrine of the patent law is better established than that a prior patent or other publication to be an anticipation must bear within its four corners adequate directions for the practice of the patent invalidated. If the earlier disclosure offers no more than a starting point for further experiments, if its teaching will sometimes succeed and sometimes fail, if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge, and it is not an anticipation."

The Fourth Circuit Court of Appeals followed a similar rule in *Binney and Smith* v. *United Carbon Co.,* 125 F. 2d 255 (reversed on other grounds). In that case, it was clear that the prior art did not disclose any manner of producing the product involved in the claim.

The rejection here amounts to the application of a doctrine which was criticized by the Circuit Court of Appeals for the Ninth Circuit in *Pacific Marine Co.* v. *A. S. Boyle Co.,* 103 F. 2d 288. There the Court held a patent invalid on the ground that what was important was the actual nature of the thing described and not the manner in which it was described. Here, likewise, we submit that the court should consider the actualities and not mere verbiage and should not consider a valuable invention anticipated merely because someone used similar terminology to describe a totally different substance in an earlier patent.

In *Cardox Corp.* v. *Armstrong Coalbreak Co.,* 194 F. 2d 376, the Seventh Circuit Court of Appeals held that a claim which read on a prior disclosure was not anticipated where the prior disclosure was inoperative. The language of the court in this connection is as follows (page 379):

> "Claiming invalidity because of lack of invention over the prior art, defendant relies heavily on Pratt patent No. 387,256; Pratt disclosed a pneumatic car-

> tridge as a propellant for ammunition. The cartridge of Pratt is shown in a gun barrel. It is operated by a hammer striking a pin to turn the control valve to venting position. While claim 2 of the Armstrong patent in suit does read upon the Pratt disclosure in several respects, it is clear that even if Pratt were operative, it was not intended for a material breaking device, except insofar as any artillery shell might damage any object with which it came into contact. No attempt was ever made to mine coal with the device. The trial court found as a fact that the device disclosed in the Pratt patent is inoperative as a coal-blasting device. That it was in fact inoperative is shown by many deficiencies appearing on the face of the patent."

The claim in the present case distinguishes over the prior art in that it names a melting point different from that disclosed and therefore would not be infringed by the material disclosed in the reference. It is submitted that since this compound has very useful and unobvious results, it should not be refused protection merely because of a misnomer applied to a prior product, where such product as disclosed would not infringe the claim.

### Estoppel

We submit that this defense is wholly without merit for a number of reasons.

In the first place, it appears on the face of the Scheuing patent (Tr. 107) that it issued to the Alien Property Custodian. Its issuance was not caused by appellant, but by this agency of the United States. And appellant has enjoyed no monopoly of any sort by reason of the issuance of the patent since, as the Patent Office admits, the practice of the Office of Alien Property was to license all German-owned patents freely upon payment of a nominal fee. How can there be any estoppel against one who has neither created the condition nor benefited from it?

And how can any estoppel arise when the patent has not existed as a monopoly at all, but has been open to the public for nothing more than a nominal service charge?

But, even if the patent were owned by appellant, there is likewise no ground for a holding of estoppel. It is quite true that, in attacking the sufficiency of the disclosure of the Scheuing patent, appellant is attacking its validity. For, clearly, if the patent give no correct procedure for producing scopolamine bromobutylate, any claim to that product is invalid. This is equally true because of the misidentification of the product as to its melting point.

But there is no estoppel, barring a contract situation not present here, against a patentee's attacking the validity of his own patent. This rule has been recognized time and again, under various circumstances.

For example, where A obtains a patent with certain claims, B copies these claims for purposes of interference, and B prevails, B will then be granted a patent containing the same claims as appear in A's patent. If B now sues A for infringement, A is not estopped to deny the validity of the claims of the B patent, even though he is thereby attacking the validity of his own patent.

That exact situation existed in *International Steel Wool Corp.* v. *Williams Co.,* 43 F. Supp. 438. The Court said (page 441):

> "Nor is defendant estopped by the interference proceedings from contesting the validity of claim 23".

Again, suppose that A has earlier and later patents. In a suit against B, B defends on the ground that the claims of the later patent are invalid for double patenting over the claims of the earlier patent. To render this defense ineffectual, A may show that the claims of the earlier patent are invalid. This was permitted in *White* v. *Converse,* 20 F. 2d 311 (Judge Learned Hand).

Likewise, the Supreme Court, in *Paramount Publix Corp.* v. *American Tri-Ergon Corp.*, 294 U.S. 464, held that a defendant was not estopped from denying the validity of a patent merely because it had itself filed an application on a similar idea and attempted to obtain similar claims.

The only authority cited by appellant in favor of this theory is *Rice-Stix Dry Goods* v. *J. D. Scriven Co.*, 165 Fed. 639. In that case, the owner of an *expired* patent, who had asserted and enjoyed a monopoly under it *for its full life*, contended that the patented feature had acquired a secondary meaning so as to have trademark significance. To rebut the argument of the defendant that the right to use the patented feature was free to all when the patent expired, the patent owner urged that the patent was actually invalid. The Court refused to accept this argument, on the ground of estoppel.

The facts of the present case are so different from those in Rice-Stix that the decision there is totally inapplicable here. In the situation now under consideration, there is an *unexpired* patent under which appellant has *neither asserted nor enjoyed* any monopoly, and the issuance of which was due to the acts of others. Surely the mere existence some fifteen years ago of a "potential" monopoly, which never came into existence, is totally immaterial.

Appellee's brief is again misleading when it speaks (page 22) of granting "the same claim" (as claim 8 of the patent) to appellant. Claim 8 of the Scheuing patent (Tr. 108) recites a compound with a melting point of *195-197°C*. Claim 10 in issue here prescribes a melting point of *142-144°C*. Thus the compound covered by claim 8 would not be the same as that specified by the claim sought in this proceeding—in other words, the claims are *not* the same, what would infringe one would *not* infringe the other, and the monopolies envisaged are different one from the other.

## CONCLUSION

We submit that the attitude of the Patent Office in this case is completely unrealistic. Claim 10 relates to a compound which has never before been actually produced—a compound which has met with substantial commercial success—a compound which has unexpected properties. The refusal to grant the patent is based on technicalities, founded on erroneous information in the prior art. In all fairness, applicant is entitled to a patent, and the decision of the District Court should be reversed.

Respectfully submitted,

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